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IN THE

Supreme Court of the United States

MYLAN INC., MYLAN LABORATORIES INC., MYLAN PHARMACEUTICALS INC. AND MATRIX LABORATORIES LTD.,

Petitioners,

v.

DAIICHI SANKYO COMPANY, LTD. AND DAIICHI SANKYO, INC.,

Respondents.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

PETITION FOR A WRIT OF CERTIORARI

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QUESTION PRESENTED

Whether, contrary to this Court's decision in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), the Federal Circuit has erred in applying a "lead compound test" as the exclusive standard for determining whether a patent claim directed to a new chemical compound is "obvious" and therefore invalid under 35 U.S.C. § 103(a).

PARTIES TO THE PROCEEDINGS AND CORPORATE DISCLOSURE STATEMENT

Petitioner Mylan Inc., formerly known as Mylan Laboratories Inc., is a publicly held corporation. Mylan Pharmaceuticals Inc. is a wholly owned subsidiary of Mylan Inc. No other parent corporations or publicly held companies own 10% or more of the stock of Mylan Inc.

Matrix Laboratories Ltd. is a privately held corporation. MP Laboratories (Mauritius) Ltd. owns a majority of stock of Matrix Laboratories Ltd., and is itself a wholly owned subsidiary of Mylan Inc. No other parent corporation or publicly held company owns 10% or more of the stock of Matrix Laboratories Ltd.

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PETITION FOR A WRIT OF CERTIORARI

Petitioners (collectively, "Mylan") respectfully petition for a writ of certiorari to review the judgment of the United States Court of Appeals for the Federal Circuit.

OPINIONS AND ORDERS BELOW

The opinion of the court of appeals (App. 1a-24a.) is reported at 619 F.3d 1346 (Fed. Cir. 2010). The opinion of the district court (App. 25a-84a.) is reported at 670 F. Supp. 2d 359 (D.N.J. 2009).

JURISDICTION

This Court has jurisdiction under 28 U.S.C. § 1254(1). The court of appeals entered judgment on September 9, 2010. No petition for rehearing was filed. The court of appeals had jurisdiction of Petitioners' appeal under 28 U.S.C. § 1295(a)(1). The district court had jurisdiction of Respondents' patent infringement claim under 28 U.S.C. § 1338(a).

STATUTORY PROVISION INVOLVED

This case concerns the standard of patentability under 35 U.S.C. § 103(a), which provides:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be

negatived by the manner in which the invention was made.

STATEMENT OF THE CASE

Diabetes. Epilepsy. Osteoporosis. Hypertension. For each of these chronic illnesses, a specific name-brand drug offers some aspect of treatment. Yet in each case, no generic equivalent exists because a patent on the branded drug claims the active ingredient as a new chemical compound.

This case presents an important issue about a legal standard applied in a significant subset of patent cases brought under the Hatch-Waxman Act.[1] The Hatch-Waxman Act established a regulatory framework by which a generic drug manufacturer can file an Abbreviated New Drug Application ("ANDA") to seek approval from the FDA to sell a generic version of an already approved drug. Most Hatch-Waxman patent cases arise when a generic drug manufacturer challenges a patent listed for an existing branded drug as being invalid for, among other reasons, obviousness. A patent claim is obvious under 35 U.S.C. § 103 if the subject matter of the claim would have been a predictable variation over the prior art by a person with ordinary skill in the relevant field. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007).

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[1] The Hatch-Waxman Act is formally known as the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (codified as amended at 21 U.S.C. § 355 and 35 U.S.C. § 271).

A troubling pattern has emerged in the Federal Circuit's Hatch-Waxman Act cases in which that court has rejected every structural obviousness challenge to a patent claiming a new chemical compound *since Congress passed the Act in 1984.* [2] This long-standing pattern has crystallized more recently with the Federal Circuit's consistent application of a "lead compound" test as the exclusive, rigid standard for determining obviousness of chemical compound patent claims. Like the teaching, suggestion, or motivation ("TSM") test that *KSR* rejected as the sole test for obviousness, the lead compound test requires a challenger to establish that one of ordinary skill in the art would have been motivated (1) to select a lead compound from the prior art to develop and (2) to make the necessary modifications to the prior art lead compound to arrive at the claimed compound. *See, e.g., Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008). This analysis was not initially intended to be a specialized obviousness test, but over time it became canonized by mechanical application in the district courts and the Federal Circuit. As applied after *KSR*, the lead compound test now stands in defiance of this Court's holding in *KSR* that the question of obviousness should be addressed with an expansive and flexible approach.

The Federal Circuit is imposing an obviousness standard for new chemical compounds that is

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[2] A "chemical compound" is "a substance formed from two or more elements chemically united in fixed proportions." Compact Oxford English Dictionary (April 2010).

analytically inflexible and practically impossible to meet. This standard indicates a disconnect between how a chemist creates new compounds and the obviousness standard used by the courts and the Patent and Trademark Office ("PTO") to determine whether that chemist's work was truly non-obvious and, thus, patent-worthy. If the standard for obviousness in these cases is overly rigid and impracticable, then the validity of every patent claim reciting the active ingredient of a branded drug will be unjustifiably unassailable under § 103(a).

Without this important defense to patent infringement claims, approval of generic equivalents of branded drugs is being delayed in cases where it should not. As a result, consumers are paying more for drugs protected by monopolies that may never have survived the scrutiny of patent law had the correct legal standard been applied. This reality contradicts the Hatch-Waxman Act's objective, evident from the official title referring to "price competition," of spurring a robust generic drug market by enforcing only valid patents on truly innovative drugs and discarding invalid patents on obvious ones. *See supra* n.1; *see also* 130 Cong. Rec. 24427 (Sept. 6, 1984) (statement of Rep. Waxman) ("A patent is a monopoly . . . as a matter of public policy we, under the patent law, give that protection to the person who has put money into research and development for an innovative new product. But at some point public policy calls for the free market system competition which will bring about the result of a lower price for the consumer. That is the purpose of the legislation.").

Instead of using the lead compound test, chemical compound patent claims should be evaluated on a case-by-case basis, with less focus on "predictability" *per se* of the claimed compound and greater focus on whether the claimed compound was "obvious to try" to a chemist of ordinary skill. Such an approach is consistent with the flexible analysis *KSR* requires, and it is especially vital in the chemical arts where, to chemists of ordinary skill, structure and activity may not be entirely predictable, but the claimed structure is obvious to try in a methodical trial-and-error process.

1. The chemical compound at issue in this case is olmesartan medoxomil, which is used alone or in combination with other drugs to treat hypertension. Olmesartan is in a class of medications known as angiotensin receptor blockers ("ARBs") and, more specifically, olmesartan is an angiotensin II ("AII") receptor antagonist. It allows blood to flow more easily through arteries by blocking certain substances from binding to the surfaces of cells. Such binding is why arteries narrow, constricting blood flow and increasing blood pressure.

2. Petitioner Mylan filed an ANDA for approval to engage in the commercial manufacture, use or sale of 5mg, 20mg, and 40mg tablets of olmesartan medoxomil, a generic equivalent of the branded drug sold by Daiichi Sankyo as Benicar®. Mylan later filed additional ANDAs on two separate combinations of olmesartan medoxomil with other compounds used to treat hypertension: a combination with hydrochloro-thiazide ("HCTZ") (sold as Benicar HCT®) and a combination with amlodipine besylate (sold as Azor®). For each ANDA, Mylan filed a

Hatch-Waxman Paragraph IV certification that its generic products would not infringe any valid claim of U.S. Patent No. 5,616,599 (the "'599 patent"), which is owned by Daiichi Sankyo. *See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV).

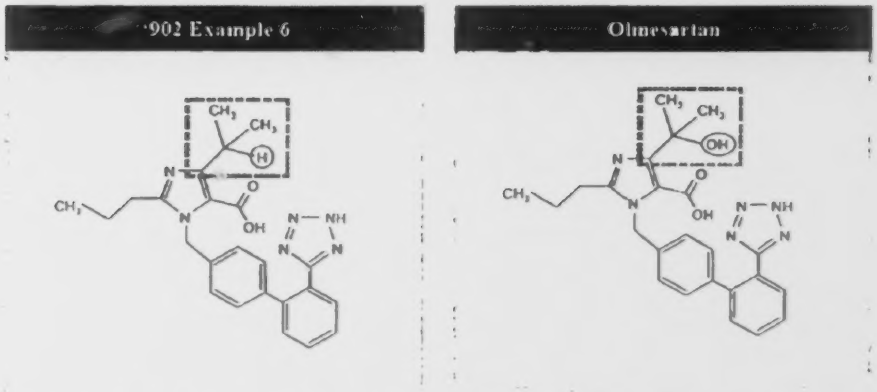
3. Pursuant to the Hatch-Waxman Act, Daiichi Sankyo filed three patent infringement suits in the United States District Court for the District of New Jersey. The three actions were consolidated and the parties stipulated that Mylan's olmesartan medoxomil products would infringe claim 13 of the '599 patent. The only issue before the court was whether claim 13 was obvious over prior art that included discoveries made by DuPont, which were in turn developed based on earlier discoveries made by the Japanese pharmaceutical company Takeda.

In the late 1970s, Takeda discovered the first AII receptor blocker. The Takeda compounds had little therapeutic value, however, as they did not work when administered orally. In 1982, DuPont used three of the Takeda compounds as models for an ARB research program. The successful result was losartan, sold under the brand name Cozaar® and the first orally active ARB to be approved by the FDA and marketed.

Losartan was disclosed by DuPont's prior art '069 patent, as were more than 400 structurally related ARBs. Subsequently, DuPont discovered ARBs with a greater oral activity than losartan. A group of six particularly active compounds were disclosed in DuPont's prior art '902 patent.

At the core of the Takeda lead compound, losartan, and later second-generation ARB compounds, was an imidazole ring. Imidazole is an

organic compound with the formula $C_3H_4N_2$. It is a common structural core used in pharmaceutical compounds. As shown below, olmesartan, the compound claimed in Daiichi Sankyo's '599 patent in suit, differs from one of DuPont's '902 compounds by *a single atom*. While olmesartan contained a hydroxyl group (–OH) at the 4-position of the imidazole ring, the '902 compound had a hydrogen atom (H) at that position:



The only other modification Daiichi Sankyo made was the addition of a medoxomil group at the 5-position of the ring. Medoxomil has been used by medicinal chemists to improve oral absorption of similar compounds well before the priority date of the '599 patent.

Following a ten-day bench trial, the district court held that, notwithstanding the minor difference between olmesartan and the prior art, Mylan failed to prove that olmesartan medoxomil was obvious in light of the prior art. A week later, the district court entered its judgment and issued an injunction prohibiting approval of Mylan's ANDA until the expiration of the '599 patent in 2016. Applying the rigid lead compound test, the district court concluded that although the Daiichi Sankyo patent applicants

admitted that the improved ARBs described in DuPont's '902 patent were the closest prior art to olmesartan, Mylan failed to show by clear and convincing evidence that a person of ordinary skill in the art of medicinal chemistry would have been motivated to select the prior art '902 compounds as lead compounds for further investigation. The court further determined that if the prior art '902 compounds were selected as lead compounds, one of ordinary skill in the art would not have been motivated to modify the lead compounds to arrive at the claimed compound because the prior art taught away from this. Thus, the court concluded that Mylan failed to establish *prima facie* obviousness.

Having already concluded that neither motivational step of the lead compound test had been satisfied, the district court went on to make the following additional findings: (a) although the only structural difference between the compounds is that the claimed compound includes an –OH group where the prior art compound has an –H atom and the addition of the well-known prodrug medoxomil, olmesartan medoxomil was not structurally similar to the '902 compound; (b) despite extensive prior use of medoxomil as a prodrug in several drugs treating hypertension and Daiichi Sankyo's admission of this fact to the PTO, the addition of the medoxomil prodrug to the olmesartan molecule was not obvious; (c) a person of ordinary skill in the art of medicinal chemistry would not have had a reasonable expectation of obtaining olmesartan medoxomil's increased oral absorption; and (d) "secondary considerations," particularly unexpected results and commercial success, overcame any *prima facie* case of obviousness. (App. 71a-73a.)

4. On appeal, the Federal Circuit affirmed the district court's decision that Mylan had failed to establish a *prima facie* case of obviousness under the lead compound test. (App. 24a.)

5. According to the court of appeals, two of its earlier decisions, *Takeda Chem. Indus. Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007), and *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369 (Fed. Cir. 2006), illustrated that "it is the possession of promising useful properties in a lead compound that motivates a chemist to make structurally similar compounds" and that the obviousness analysis "requires the challenger to demonstrate by clear and convincing evidence that one of ordinary skill in the art would have had a reason to select a proposed lead compound or compounds over other compounds in the prior art." (App. 17a-18a.) The Federal Circuit declined to review the district court's additional findings.[3] (App. 24a.)

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[3] The district court's additional findings were made in the context of its not having found a *prima facie* case of obviousness as a result of its erroneous lead compound approach. Evaluation of each of these additional findings depends upon the strength of the *prima facie* case on obviousness. If this Court agrees with Petitioners that the Federal Circuit erred in applying a lead compound test instead of taking the flexible approach mandated in *KSR*, then the proper result would be to vacate the Federal Circuit decision and remand for consideration of all facets of the obviousness question in the proper legal context.

REASONS FOR GRANTING THE WRIT

I. Like the TSM Test that *KSR* Rejected, the Lead Compound Test Is Too Rigid and Sets an Impossibly High Standard for Obviousness in Chemical Compound Cases.

Patent claims asserted in Hatch-Waxman litigation are generally directed to one of a few categories of subject matter, such as new chemical compounds, specific configurations of known compounds (i.e., stereoisomers[4]), pharmaceutical formulations of known compounds, methods of using or preparing a compound, and methods of treating a medical condition. How an asserted claim is drafted determines the category into which it falls. Within these categories, new chemical compound claims are peculiar in that when they are challenged as being invalid for obviousness under 35 U.S.C. § 103, Federal Circuit case law requires that they be evaluated under a special obviousness analysis not applicable to any of the other categories: the "lead compound" test.

To establish a claimed chemical compound as obvious over the prior art under the lead compound test, a challenger must prove that one of ordinary skill in the art would have chosen the closest prior art as a "lead compound" and that the modification of the

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[4] Stereoisomers are compounds that contain the same constituent atoms and the same bonding between those atoms but have different spatial arrangements. *Forest Labs., Inc. v. Ivax Pharms., Inc.*, 501 F.3d 1263, 1265 (Fed. Cir. 2007).

lead compound to arrive at the claimed compound was obvious. Like the rigid TSM test that *KSR* rejected as the sole test of obviousness, the lead compound test requires a challenger to establish that one of ordinary skill in the art would have been motivated in two specific ways: (1) to select the lead compound and (2) to modify the lead compound to arrive at the claimed compound.[5] The two parts are not alternatives; a challenger must satisfy both prongs to establish a *prima facie* case of obviousness.

This Court explained in *KSR* that obviousness in *all* patent cases should be evaluated by a flexible test. 550 U.S. at 415, 419 (explaining that throughout the Court's engagement with the question of obviousness, its decisions have set forth "an expansive and flexible approach" effected by "broad inquiry" rather than "rigid and mandatory formulas" and particularized tests). The Federal Circuit has disregarded this guidance and continues to apply the same lead compound test to all new chemical compound claims as an inflexible rule. *See, e.g.*, *Eisai*, 533 F.3d at 1359 ("[P]ost-*KSR*, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound.").

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[5] *See, e.g.*, *Takeda*, 492 F.3d at 1357 (affirming nonobviousness where the district court determined that the challenger "failed to adduce evidence that compound b would have been selected as the lead compound and, even if that preliminary showing had been made, it failed to show that there existed a reason, based on what was known at the time of the invention, to perform the chemical modifications necessary to achieve the claimed compounds").

Applying the lead compound test rigidly, the Federal Circuit has found nonobviousness in *each and every* chemical compound patent case since *KSR*. In contrast, for example, the court has found two out of three pharmaceutical method-of-treatment patents obvious over the same time period. As the following table demonstrates, the Federal Circuit is effectively applying a much higher standard to chemical compounds than it does to other inventions, even within the chemical arts.[6]

Category	Case / Compound	Conclusion
Chemical Compound	*Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007) / pioglitazone (to treat type II diabetes)	Not obvious
Chemical Compound	*Eisai Co. Ltd. v. Dr. Reddy's Labs., Inc.*, 533 F.3d 1353 (Fed. Cir. 2008) / rabeprazole (to treat ulcers)	Not obvious
Chemical Compound	*Ortho-McNeil Pharma., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358 (Fed. Cir. 2008) / topiramate (to	Not obvious

[6] The table does not include *Altana Pharma AG v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 999 (Fed. Cir. 2009), a chemical compound case in which the Federal Circuit affirmed the district court's denial of a preliminary injunction, because the Federal Circuit did not rule on the merits of the defense.

	treat seizures)	
Chemical Compound	*Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989 (Fed. Cir. 2009) / risedronate (to treat osteoporosis)	Not obvious
Chemical Compound	*Daiichi Sankyo v. Matrix Labs.*, 619 F.3d 1346 (Fed. Cir. 2010) / olmesartan (to treat hypertension)	Not obvious
Compared With		
Method of Treatment	*Daiichi Sankyo v. Apotex*, 501 F. 3d 1254 (Fed. Cir. 2007)	Obvious
Method of Treatment	*PharmaStem Therapeutics v. Viacell, Inc.*, 491 F.3d 1342 (Fed. Cir. 2007)	Obvious
Method of Treatment	*Eli Lilly & Co. v. Teva Pharms. USA, Inc.*, 619 F.3d 1329 (Fed. Cir. 2010)	Not obvious

In *Takeda*, the Federal Circuit affirmed the district court's nonobviousness determination. 492 F.3d at 1359. The Federal Circuit stated that its pre-*KSR* precedent regarding structural similarity required defendants to establish that the "prior art would have *suggested* making the *specific* molecular modifications necessary to achieve the claimed invention," *id.* at 1356 (emphasis added), or that there was "adequate support in the prior art" of some "*reason* or *motivation*" to make the claimed

compound, *id.* (emphasis added). Although this Court rejected the "rigid and mandatory" TSM formula in *KSR*, the Federal Circuit reasoned that this precedent was consistent with *KSR* and further stated that "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." *Id.* at 1357. The Federal Circuit specifically rejected defendant's arguments that a nonobviousness determination was contrary to *KSR* because the identified lead compound ("compound b") was within "the objective reach of the claim" and the evidence demonstrated that using the techniques of homologation and ring-walking would have been "obvious to try." *Id.* at 1359. The court reasoned that the "obvious to try" argument failed because the prior art did not "identify predictable solutions for antidiabetic treatment," that the choice of compound b as a lead compound was not clear, and certain negative properties of compound b would have taught away from its choice as a lead compound. *Id.*

In *Eisai*, Teva argued that the claimed compound was obvious over the combination of three references that disclosed prior art compounds lansoprazole and omeprazole. 533 F.3d at 1357. Teva asserted that one of ordinary skill in the art would have been motivated to start with lansoprazole as a lead compound because it was structurally identical to the claimed compound but for one substituent on its pyridine ring. *Id.* Citing *Takeda*, the Federal Circuit explained that this Court's analysis in *KSR* relied on several assumptions regarding the prior art landscape and that "*KSR* presupposes that the record

up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound." *Id.* at 1359. The court found that the record showed "no discernible reason for a skilled artisan to begin with lansoprazole only to drop the very feature . . . that gave [it its] advantageous property" of being lipophilic. *Id.* at 1358.

In *Ortho-McNeil*, the Federal Circuit determined that there was nothing in the record showing that (i) an ordinarily skilled artisan who sought to develop the same type of anticonvulsant as the claimed compound would have started with the prior art compound the inventor started with, (ii) the artisan would have had "some reason to select (among several unpredictable alternatives) the exact route that produced" the claimed compound as an intermediate, or (iii) the artisan would have had any reason to stop at the intermediate and test it for properties far afield from the purpose for the development (i.e., epilepsy rather than diabetes). 520 F.3d at 1364.

In *Procter & Gamble*, the Federal Circuit determined that even if the identified lead compound was selected as a lead compound, the evidence did not establish that it would have been obvious to a person of ordinary skill in the art to modify it to create the claimed compound. 566 F.3d at 995. According to the court, the properties of bisphosphonates, which included both the lead compound and the claimed compound, could not be anticipated based on their structure. *Id.* at 996. The court supported this "unpredictability" finding by noting that plaintiff had synthesized three structural isomers of the claimed

compound—the lead compound, the claimed compound, and a third compound—and found the third compound "was not active in inhibiting bone resorption despite its close relationship with potent compounds." *Id.* In view of this unpredictability and "an insufficient showing that a person of ordinary skill in the art would have had a 'reasonable expectation of success' in synthesizing and testing the claimed compound, the Federal Circuit determined "there [wa]s no credible evidence that the structural modification was routine" and, therefore, the claimed compound was not obvious. *Id.*

In this case, *Daiichi Sankyo*, the Federal Circuit determined that Mylan failed to show that one of ordinary skill in the art would have been motivated to select the ARBs disclosed in the DuPont '902 patent as lead compounds and, even if the '902 ARBs had been selected as lead compounds, Mylan failed to show that a skilled artisan would have been motivated to modify them to synthesize the claimed compound. (App. 15a.) Specifically, the Federal Circuit affirmed the district court's finding that even though the '902 ARBs "'exhibit[ed] remarkable and unexpected potency as antihypertensives,'" the prior art included even more potent antihypertensives such that a medicinal chemist of ordinary skill would not have been motivated to choose the '902 ARBs over the more potent compounds. (App. 16a.) (quoting *Daiichi Sankyo Co., Ltd. v. Mylan Pharms. Inc.*, 670 F. Supp. 2d 359, 376 (D.N.J. 2009)). The Federal Circuit reasoned that "[p]otent and promising activity in the prior art trumps mere structural relationships." (App. 17a.)

Regarding the motivation to modify the lead compounds, the Federal Circuit found that even if the medicinal chemist of ordinary skill chose the '902 ARBs as lead compounds, the prior art taught away from the use of a hydrophilic substitute at the 4-position of the imidazole ring because, among other reasons, "[t]he few compounds [in the prior art] with hydrophilic groups at the 4-position are drowned out by the sea of 4-lipophilic compounds." (App. 19a.) Further, the court found, the '902 ARBs would be attractive as lead compounds specifically because they included lipophilic alkyl groups at the 4-position and "'a person of ordinary skill in the art would not select the '902 patent compounds as leads only to disregard one of their distinguishing characteristics.'" (App. 23a (quoting *Daiichi Sankyo*, 670 F. Supp. 2d at 379).) Lastly, the Federal Circuit stated that even if the prior art did not teach away from the hydrophilic group at the 4-position, the prior art "simply does not provide a reason to make such a modification." (App. 23a.)

Each of these cases is substantively unique, and there is no compelling reason to apply a single, inflexible test to them. In spite of *KSR*'s rejection of such an approach (which is analogous to the TSM test), the Federal Circuit continues to apply the same flawed lead compound test in all its post-*KSR* chemical compound cases. *KSR*, 550 U.S. at 419 ("The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents.").

II. Rigid Application of the Lead Compound Test Undermines Fundamental Policies of the Patent and Drug Laws.

The underlying goal of the Hatch-Waxman Act is to preserve incentives to engage in research and development while promoting the wider availability of generic drugs.[7] In cases involving chemical compound patents, this policy is achieved when a finding of nonobviousness is reserved for truly innovative discoveries, as opposed to incremental developments over the prior art. Yet the opposite is occurring, indicating a trend whereby courts are overly reluctant to reach a conclusion of obviousness in chemical compound cases, regardless of whether

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[7] *Teva Pharms. USA v. Pfizer, Inc.*, 405 F.3d 990, 995 (Fed. Cir. 2005) ("The [Hatch-Waxman Act] provides an express mechanism for generics to challenge, with declaratory actions, the claim scope or validity of listed patents. Under this statutory scheme, it is court challenges by generic drug companies that limit incumbent overreaching by submitting over-inclusive lists of patents applicable to any given branded formulation."); *see also* Hearing on H.R. 1706 Before the H. Subcomm. on Commerce, Trade, and Consumer Protection, 111th Cong., 10 (Mar. 31, 2009) (statement of Subcomm. Chair Hon. Bobby L. Rush) ("As a carrot to encourage patent challenges, the Hatch-Waxman Act provides the first filer 180 days of exclusivity as the only generic drug permitted on the market, simply enabling a successful generic company challenger to recoup its significant litigation costs. It is this reward that encourages the risk of challenging a patent. If this exclusivity is no longer granted, the result will be the opposite of what this bill intends. Fewer drugs patents will be challenged, and consumers will have to wait much longer until patents expire or litigation come to conclusion before cheaper generic drugs can be made available.").

the claimed compound results from a minor modification to a known compound that, while perhaps not obvious to a lay person, is well within the ability and insight of a chemist of ordinary skill.[8]

This trend contradicts the expansive and flexible approach to evaluating obviousness that this Court required in *KSR*:

> The diversity of inventive pursuits and of modern technology counsels against limiting the analysis [in a formalistic manner]. Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, in the case of patents combining previously known elements, deprive prior inventions of their value or utility.

550 U.S. at 418; *see also* U.S. Fed. Trade Comm'n, To Promote Innovation: The Proper Balance of Competition and Patent Law and Policy 6 & n.23 (2003), *available at* http://www.ftc.gov/os/2003/10

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[8] *Compare Perfect Web Technologies, Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1328 (Fed. Cir. 2009) (holding a claimed method for managing bulk e-mail distribution to be obvious where there was a "finite number of identified, predictable solutions" and the supposedly inventive step was "obvious to try because there were, at most, two or three predictable solutions at the time for ensuring e-mail delivery.") *with Takeda*, 492 F.3d at 1359 (Fed. Cir. 2007) (rejecting the argument that the claimed compounds were obvious despite the fact that the lead compound fell within the objective reach of the claim and evidence demonstrated that the techniques of homologation (replacing a methyl group with an ethyl group) and ring-walking (moving the ethyl substituent to another position on the ring) would have been "obvious to try" to one ordinarily skilled in the art.).

/innovationrpt.pdf (discussing how a restrictive obviousness standard can result in unwarranted market power that delays competition).[9]

The *quid pro quo* of patent protection is that in exchange for disclosure to the public of a novel and nonobvious invention, the patentee receives exclusive rights to the invention for a limited time. *See* U.S. Const., art. 1, § 8. In the context of this exchange, patentability standards like nonobviousness under 35 U.S.C. § 103 take on heightened significance in drug discovery because an overly strict application of the analyses used to test alleged inventions against these standards results in unchallengeable patents on marginal developments over the prior art that hinder rather than promote the progress of science.

Nowhere is the impact of patent law on the public interest more apparent than in Hatch-Waxman cases. Yet, despite a constitutional mandate that patents be issued only for truly innovative inventions, explicit Congressional intervention to promote a robust generic drug market, and clear Supreme Court precedent requiring flexibility and case-by-case analysis, the Federal Circuit has not found even a single chemical compound claim to be obvious since

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[9] *Accord Abbott Labs. v. Sandoz, Inc.*, 544 F.3d 1341, 1352 (Fed. Cir. 2008) ("The methodology of science and the advancement of technology are founded on the investigator's educated application of what is known, to intelligent exploration of what is not known. Each case must be decided in its particular context, including the characteristics of the science or technology, its state of advance, the nature of the known choices, the specificity or generality over the prior art, and the predictability of results in the area of interest.").

enactment of the Hatch-Waxman Act. Meanwhile, the high cost of drugs forces the afflicted to skip needed doses. *See* John D. Piette et. al., *Cost-Related Medication Underuse Among Chronically Ill Adults: the Treatments People Forgo, How Often, and Who Is at Risk*, Am J Public Health (2004).

This trend is further perpetuated by the PTO's adoption of the lead compound analysis in its 2010 PTO Guidelines for patent examiners. Examination Guidelines Update: Developments in the Obviousness Inquiry After KSR v. Teleflex, 75 Fed. Reg. 53,643 (Sept. 1, 2010) ("2010 PTO Guidelines"), *available at* http://edocket.access.gpo.gov/2010/pdf/2010-1646.pdf. Although the PTO mentions that six rationales in addition to the TSM test can be used to support an obviousness determination, most of the chemical compound cases appear under the lead compound analysis. Without direction from Congress or this Court to refrain from an overly rigid lead compound analysis, the infection that pervades the courts will continue to spread through the PTO as well.

Finally, although the patent law treatment of chemical compounds may seem to be a technical concept best suited for specialized determination by the PTO and the Federal Circuit, the public and the government ultimately incur the expense of delayed action, and Supreme Court inaction, on this issue. Indeed, when signing the Hatch-Waxman Act into law, President Reagan emphasized "the American people will benefit, because the Federal Government, the largest single consumer of drugs, will be able to purchase generic drugs at significantly lower cost." Remarks on Signing S. 1538 Into Law, 20 Weekly Comp. Pres. Docs. 1349, 1360 (Sept. 24, 1984) (noting

that in 1983 the government spent $2.4 billion on drugs for Medicaid, veterans and military hospitals). Since the passage of the Act, government expenditures on prescription drugs have only increased. *See, e.g.*, Congressional Budget Office, Effects of Using Generic Drugs on Medicare's Prescription Drug Spending vii (2010), *available at* http://www.cbo.gov/ftpdocs/118xx/doc11838/09-15-PrescriptionDrugs.pdf (approximating that, in 2007, $60 billion was spent on drug prescriptions for the Medicare Part D program, of which 30% was filled with branded drugs).

That no patents for drugs claiming chemical compounds have been held invalid for obviousness since the passage of the Act indicates that the policies of the Hatch-Waxman Act are being undermined by the prevailing legal analysis.

III. The Lead Compound Test Has Been Flawed Since Its Inception and Should Be Replaced with a Flexible, Case-By-Case Basis Analysis.

a) The lead compound test was an accident.

The lead compound test is the result of an unchecked propagation of error in Federal Circuit case law that only this Court can remedy. The test has origins in (1) a loose statement that was made in *Yamanouchi v. Danbury*, 231 F.3d 1339, 1345 (Fed. Cir. 2000), and implicitly adopted in *Eli Lilly*, 471 F.3d at 1377-79, regarding the selection of a lead compound; and (2) dicta in *Takeda*, 492 F.3d at 1357 that "in cases involving new chemical compounds, it

remains necessary to identify some reason that would have led a chemist to modify a known compound."

The lead compound concept was first discussed in *Yamanouchi* not as a test but as a rejection of an argument made by the defendant to support its theory of obviousness. The *Yamanouchi* opinion explained how each step of defendant's multi-step theory of how a skilled artisan could have used the prior art to arrive at the claimed compound did not work. Beginning its analysis with defendant's first argument that it was obvious to select a certain reference as a lead to make the claimed compound, the court stated: "[a]t the outset, [defendant] did not show the *required motivation for selecting example 44 as a lead compound*." *Id.* at 1344-45 (emphasis added). The "required motivation" language referred to an argument made by defendant that it would have been obvious to a person ordinarily skilled in the art to take three particular steps to create the claimed compound, the first of which was to select a compound from an earlier patent as a "lead compound."

While not intended to be applied as a firm rule, this statement was cited subsequently by district courts for the proposition that "[d]efendants must establish by clear and convincing evidence that one of ordinary skill in the art would have been motivated to select [the closest prior art compound] as a lead compound." *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 364 F. Supp. 2d 820, 904 (S.D. Ind. 2005). On appeal, the Federal Circuit noted, but did not address, defendants' argument that the district court had erred by erecting a "threshold requirement that defendants establish a teaching or incentive to

treat the closest prior art . . . as a lead compound." 471 F.3d. at 1377. Instead, the Federal Circuit highlighted the similarities between the case before it and *Yamanouchi* because in both situations the "defendants ha[d] not shown that a person ordinarily skilled in this art would have selected [the closest prior art compound] as a lead compound." *Id.* at 1379.

In this manner, although case law never discussed a requisite showing of motivation to select a lead compound, a statement in *Yamanouchi* that was never intended to establish a rule was implicitly adopted by *Eli Lilly* and mistakenly interpreted as doctrine. *See, e.g., Eisai Co., Ltd. v. Teva Pharms. USA, Inc.*, No. 03-civ-9223, 2006 U.S. Dist. LEXIS 73516, at *23 (S.D.N.Y. Oct. 5, 2006); *Takeda Chem. Indus. v. Mylan Labs., Inc.*, 459 F. Supp. 2d 227, 242 (S.D.N.Y. 2006).

b) The lead compound test is rooted in and suspectible to the same misuse as the TSM test.

While *Yamanouchi* shows the lead compound concept was not intended to be a rule, *Takeda* shows that the fundamental problem with its adoption as a rule is that it was rooted in the TSM test that *KSR* just two months prior had warned should only be applied *flexibly*. Discussing *KSR*, *Takeda* noted that it remained important to identify "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does." 492 F.3d at 1356-57 ("As long as the [TSM] test is not applied as a rigid and mandatory formula, that test can provide helpful insight to an obviousness inquiry.") (internal

quotation marks omitted). Although the Federal Circuit reiterated *KSR*'s warning that overly rigid tests are not to be used in an obviousness analysis, the court did not heed the warning in that case or in the chemical compound cases that followed. *See, e.g., Eisai*, 533 F.3d at 1356-57 (citing to *Takeda* for the rule that "[o]bviousness based on structural similarity thus can be proved by identification of some motivation that would have led one of ordinary skill in the art to select and then modify a known compound (i.e. a lead compound) in a particular way to achieve the claimed compound."); *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (citing to *Eisai.* and *Takeda* for the same); *Altana*, 566 F.3d at 1007 (citing *Takeda* and *Yamanouchi* for the same).

Indeed, the analysis the Federal Circuit applied before *Yamanouchi* more appropriately recognized that flexibility is necessary in the chemical arts. In *In re Dillon*, the court of appeals reaffirmed that *prima facie* obviousness in chemical compound cases can be established by demonstrating (1) structural similarity between the claimed and prior art compositions and (2) motivation to make the new composition. 919 F.2d 688, 692-93 (Fed. Cir. 1990). The court cautioned, however, that:

> *Each situation must be considered on its own facts*, but it is not necessary in order to establish a *prima facie* case of obviousness that both a structural similarity between a claimed and prior art compound (or a key component of a composition) be shown and that there be a suggestion in or expectation from the prior art that the claimed compound

> or composition will have the same or a similar utility as one newly discovered by applicant.

Id. (emphasis added) (citation omitted). In short, *Dillon* stressed that it "is not the law" that a *prima facie* obviousness rejection must be supported by a reference showing or suggesting newly discovered properties. *Id.*

c) The lead compound test should be abandoned for a more flexible analysis that focuses less on "predictability" *per se*.

In its post-*KSR* chemical compound cases, the Federal Circuit has used the perceived "unpredictability" of medicinal chemistry to support its underlying rigid application of the lead compound rule. To be sure, *KSR* stressed "predictability" as a theme courts should consider seriously in analyzing obviousness. However, *KSR* was also clear that the perspective from which predictability should be evaluated is always that of the person of ordinary skill in the relevant art. Evaluating obviousness from this perpsective on the facts of each case is the only way to ensure that the appropriate standard of predictability is met.

In fields where those of ordinary skill routinely manage unpredictability, the obviousness analysis should focus less on "predictability" *per se* and more on whether the alleged invention was "obvious to try," another theme stressed by *KSR*. This type of subject matter-sensitive calibration of the obviousness analysis is consistent with the flexible case-by-case analysis *KSR* requires. This type of analysis is especially vital in the chemical arts where, to medicinal chemists of ordinary skill, the result of

combining certain structural features or substituents may not be entirely predictable, but their combination is "obvious to try" in a laboratory where properties of compounds are tested day after day in the methodical trial-and-error process that is the mainstay of chemical synthesis. Predictability is a highly relative term because experience and specialized knowledge often yield inferences that are anticipated in some arts and not in others.

In *KSR*, this Court expressly noted that it was error for the Federal Circuit to conclude that a patent claim cannot be proved obvious merely by showing that it was obvious to try. *KSR*, 550 U.S. at 421. Nonetheless, the Federal Circuit appears to be resistant to the obvious to try rubric and has found it inapplicable in several situations. For example, it has refused to apply it where there are a multitude of ways to solve a problem, where no "reason" exists to make a modification, and where there is no "predictability" of success in a combination. *KSR* expressly contemplated that "the fact that a combination was obvious to try might show that it was obvious under § 103." *Id.*

In line with this principle, both the 2007 and 2010 PTO Guidelines list an "obvious to try" analysis as one of six rationales that, per *KSR*, can support a determination of obviousness. 2010 PTO Guidelines, 75 Fed. Reg. 53,643, 53,644. As to when and how this approach should be used, this Court's guidance was that:

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good

> reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

KSR, 550 U.S. at 421 (emphasis added).

Elaborating on the definition of "obvious to try" the PTO Guidelines require a two–part showing that the skilled artisan (1) have chosen "from a finite number of identified, predictable solutions" and (2) did so with "a reasonable prediction of success." PTO Guidelines at 53,644. While the first part of the PTO's description has roots in the "predictable solutions" language used by the Supreme Court in *KSR*, the latter portion of the PTO's description was recently emphasized by the Federal Circuit in *In re Kubin* as indicative of what a skilled artisan would have expected in light over the prior art. 561 F.3d 1351, 1360-61 (Fed. Cir. 2009).

Thus, although last year the Federal Circuit in *Kubin* noted that this Court in *KSR* resurrected the obvious to try rationale, the Federal Circuit still refuses to use the obvious to try defense in chemical compound cases. Instead, the Federal Circuit has exclusively applied the lead compound analysis to such cases because of "unpredictability." The danger of using such an approach is that it ignores the wealth of detail that can potentially separate each case on its facts. And in cases like this case, where there was a well developed record establishing what was routine from the perspective of a medicinal chemist, the finding of nonobviousness was "likely the product not of innovation but of ordinary skill and common sense . . . [where] the fact that a combination

was obvious to try might [have shown] that it was obvious under § 103." *Id.*

IV. This Case Is An Appropriate Vehicle for Resolving the Question Presented.

This case provides a prime opportunity for this Court to consider whether the lead compound test is inconsistent with *KSR*.

First, the lead compound test has become ingrained in Federal Circuit case law as the exclusive test to be applied in all new chemical compound cases. As such, the test is widely used by district courts throughout the country, even by those courts that recognize that the statement made by the Federal Circuit in *Yamanouchi* was "not the creation of a new legal requirement, but merely a factually-specific application of the 'motivation-suggestion-teaching' test." *Janssen Pharmaceutica N.V. v. Mylan Pharms., Inc.*, 456 F. Supp. 2d 644, 657 n.4 (D.N.J. 2006).

Second, as the history of the lead compound test demonstrates, *Eli Lilly*, a pre-*KSR* case using the TSM test, and *Takeda*, a post-*KSR* case utilizing the TSM test, have played an important role in perpetuating a cramped view of *KSR*'s intention with respect to flexibility in an obviousness analysis. Both cases were submitted to this Court for review of whether the Federal Circuit had applied the TSM test in a manner inconsistent with the flexible approach advocated in *KSR*. And in both situations, certiorari was denied. *Eli Lilly*, 471 F.3d. 1369, cert. denied, *Teva Pharms. USA, Inc. v. Eli Lilly & Co.*, 552 U.S. 941 (2007); *Takeda*, 492 F.3d 1350, cert. denied, 552 U.S. 1295 (2008). Denial of certiorari in

Eli Lilly and *Takeda* bolsters the justification for granting certiorari in this case. That this case follows *Eli Lilly* and *Takeda* exemplifies how the lead compound test has evolved over the years into a standard that can never be met.[10]

Third, because the Federal Circuit has exclusive jurisdiction over patent appeals, unless this Court intervenes, the law of obviousness as applied to new chemical compounds will not change. Just as it has occurred since 1984, the Federal Circuit will continue to reject every obviousness challenge of a patent claiming a new chemical compound for the sole reason that the lead compound test is impracticable to meet. Although chemical compound cases may seem arcane and inaccessible, this is not a reason to deny certiorari. At its heart, the subject matter of new chemical compound claims involves medicine. Millions of individuals have chronic ailments that

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[10] Mylan asserted in the Federal Circuit that, post-*KSR*, it is legal error to apply the obviousness standard in an overly rigid manner. The court nonetheless refused to flexibly construe the lead compound analysis. Specifically, the court disregarded its own statement in *Altana Pharma AG v. Teva Pharmaceuticals. USA, Inc.*, 566 F.3d 989, 1008 (Fed. Cir. 2009), that a "restrictive view of the lead compound test would present a rigid test similar to the teaching-suggestion-motivation test that [this Court] explicitly rejected in *KSR*," and found that the lead compound analysis "still requires the challenger to demonstrate by clear and convincing evidence that one of ordinary skill in the art would have had a reason to select a proposed lead compound or compounds." (App. 18a (emphasis added).) Such an express refusal by the Federal Circuit to follow *Altana* provides this Court with another reason to review this important legal standard.

cannot be cured but can be treated with proper medication. The purpose of the Hatch-Waxman Act is not served if they cannot access *affordable* medication because of an overly rigid legal test.

Fourth, an alternative to the lead compound test has already been advocated in case law, but the Federal Circuit has resisted it. In fields where those of ordinary skill routinely manage unpredictability, the obviousness analysis should focus less on "predictability" *per se* and more on whether the alleged invention was "obvious to try," another theme stressed by *KSR*.

In short, until this Court speaks, its guidance in *KSR* will be disregarded in this important area of medicinal chemistry. The lead compound test will continue to "stifle, rather than promote, the progress of useful arts." *Id.* at 427. Instead of waiting for yet another challenge on this same ground, the Court should take this case.

CONCLUSION

The petition for a writ of certiorari should be granted.

Respectfully submitted,

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December 8, 2010

APPENDIX

APPENDIX A — DECISION OF THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT DECIDED SEPTEMBER 9, 2010

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

DAIICHI SANKYO COMPANY, LTD.,
AND DAIICHI SANKYO, INC.,

Plaintiffs/Counterclaim
Defendant-Appellees,

v.

MATRIX LABORATORIES, LTD., MYLAN INC.,
MYLAN LABORATORIES, INC., AND
MYLAN PHARMACEUTICALS, INC.,

Defendants-Counterclaimant-Appellants.

2009-1511

Appeal from the United States District Court for the District of New Jersey in Case No. 06-CV-03462, Judge William J. Martini.

Decided: September 9, 2010

Appendix A

DOMINICK A. CONDE, Fitzpatrick, Cella, Harper & Scinto, of New York, New York, argued for plaintiffs/counterclaim defendant-appellees. With him on the brief were lisa b. Pensabene and JOSHUA I. ROTHMAN. Of counsel on the brief were HENRY B. GUTMAN, ROBERT A. BOURQUE and NOAH M. LEIBOWITZ, Simpson Thacher & Bartlett LLP, of New York, New York.

ROBERT L. BYER, Duane Morris LLP, of Pittsburgh, Pennsylvania, argued for defendants/counterclaimant-appellants. Of counsel on the brief were SHANNON M. BLOODWORTH, Perkins Coie LLP, of Washington, DC, and DAVID J. HARTH, The Law Office of David J. Harth, of Madison, Wisconsin. Of counsel was DAN L. BAGATELL, Perkins Coie Brown & Bain P.A., of Phoenix, Arizona.

Before LOURIE, FRIEDMAN, and LINN, *Circuit Judges*. LOURIE, *Circuit Judge*.

Matrix Laboratories, Ltd., Mylan Inc., Mylan Laboratories, Inc., and Mylan Pharmaceuticals, Inc. (collectively, "Mylan") appeal from the final decision of the United States District Court for the District of New Jersey sustaining the validity of U.S. Patent 5,616,599 ("the '599 patent") under 35 U.S.C. § 103. We affirm.

Appendix A

BACKGROUND

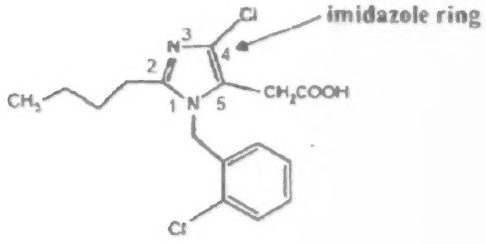
I.

Daiichi Sankyo Company, Ltd. and Daiichi Sankyo, Inc. (collectively, "Daiichi") own the '599 patent, which claims 1-biphenylmethylimidazole compounds and their use as angiotensin receptor blockers ("ARBs") for the treatment of high blood pressure. Claim 13 of the '599 patent covers the chemical compound olmesartan medoxomil, an ARB approved by the Food and Drug Administration ("FDA") and commercialized by Daiichi as the active ingredient in Benicar®, Benicar HCT®, and Azor®.

The invention of olmesartan medoxomil as an effective ARB built on years of research beginning in the 1970s, when scientists first came to appreciate the role of the angiotensin protein in controlling blood pressure. The first non-protein, small molecule ARBs were developed in the late 1970s and early 1980s by the Japanese pharmaceutical company Takeda Pharmaceutical Co. Ltd. ("Takeda"). These compounds each comprised an imidazole ring—a five-membered ring of the formula $C_3H_4N_2$—to which other chemical moieties were bonded at the 1-5-positions of the ring. One Takeda compound, S-8307, possessed a chlorophenyl group bonded through a methylene group at the 1-position, a butyl group (-C_4H_9) at the 2-position, a chlorine atom (-Cl) at the -position, and an acetic acid moiety (-CH_2COOH) at the -position. The chemical

Appendix A

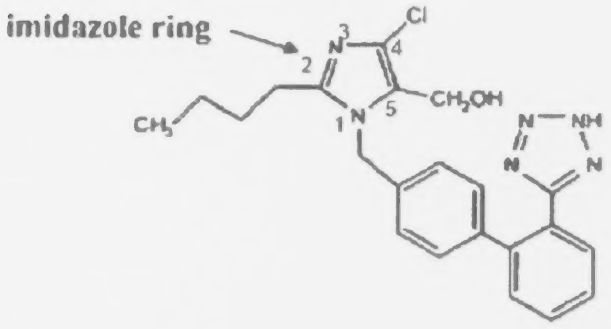
structure of S-8307 is pictured below with the ring's 1-position nitrogen positioned at the bottom of the ring.



S-8307
(Takeda)

The Takeda compounds, however, bound only weakly to the angiotensin receptor and thus were of little therapeutic value. Nevertheless, using Takeda's compounds as leads, scientists at E. I. du Pont de Nemours and Company ("DuPont") embarked on their own ARB research program with the aim of developing new compounds with increased receptor-binding activity. DuPont's research led to the discovery of the first orally active ARB, known as losartan, which exhibited ten-fold greater binding affinity than the Takeda compounds. To obtain losartan, DuPont modified Takeda's S-8307 at the 1- and 5-positions of the imidazole ring: At the 1-position, DuPont added a second phenyl group with a tetrazole group attached, generating a biphenyltetrazole substituent. At the 5-position, DuPont replaced the acetic acid group with a

hydroxymethyl group (-CH_2OH), which is metabolized to a carboxylic acid (-COOH) in the body. The chemical structure of losartan is depicted below.



LOSARTAN
(DuPont)

DuPont disclosed losartan in U.S. Patent 5,138,069 ("the '069 patent") along with more than four hundred structurally related ARBs. The '069 patent also discloses binding affinity data, measured as IC_{50} values,[1] for over two hundred compounds, including forty-two in losartan's biphenyltetrazole series. Chemists were

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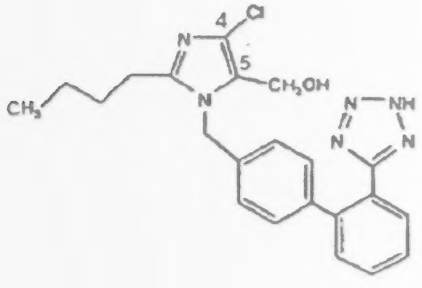
1. The half maximal inhibitory concentration, or IC_{50}, represents the concentration of an inhibitor that is required for 50% inhibition of its target, and thus the effectiveness of an inhibitor. More specifically, a lower IC_{50} indicates a higher affinity binding.

able to use the data disclosed in the '069 patent to uncover correlations between the compounds' structures and their binding affinities, called "structural-activity relationships" ("SARs"), which they could then use to guide the development of even more potent ARBs. For example, if the presence of a certain chemical moiety or type of chemical moiety at a given position correlates with an increase in binding affinity, chemists could attempt to use that chemical moiety or type of moiety in the next generation of ARBs, and they did.

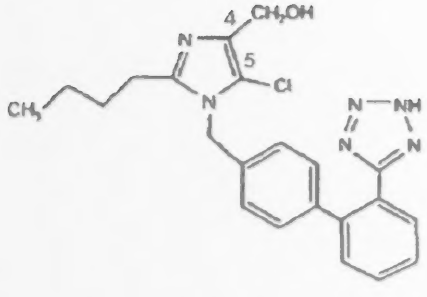
Following losartan's success, over twenty different pharmaceutical companies, including Daiichi, established research programs to develop the next generation of ARBs. Daiichi's program resulted in the synthesis of olmesartan, the active metabolite of olmesartan medoxomil. Like losartan, olmesartan consists of an imidazole ring containing a biphenyltetrazole substituent at the 1-position and an alkyl group (propyl rather than butyl) at the 2-position. At the 4-position, however, olmesartan replaced losartan's lipophilic, or fat-loving, chlorine atom with its opposite, a hydrophilic, or water-loving, hydroxyisopropyl group ($-C(CH_3)_2OH$).[2] Of the compounds disclosed in DuPont's '069 patent, the vast majority

2. When one speaks of replacing one group with another, it is understood that the "replacement" is not accomplished merely by writing it on paper and that an actual change from one group to another more often occurs by a new synthesis using different starting materials, *i.e.*, a chlorine atom is not directly replaced with a hydroxyisopropyl group.

contain a lipophilic group at the ring's 4-position. One compound with a hydrophilic group is losartan's regioisomer,[3] Example 118, in which the 4- and 5-positions on the imidazole ring are reversed. The transposition results in a compound with a chlorine atom at the 5-position and a hydrophilic hydroxymethyl group ($-CH_2OH$) at the 4-position, as shown below.



LOSARTAN

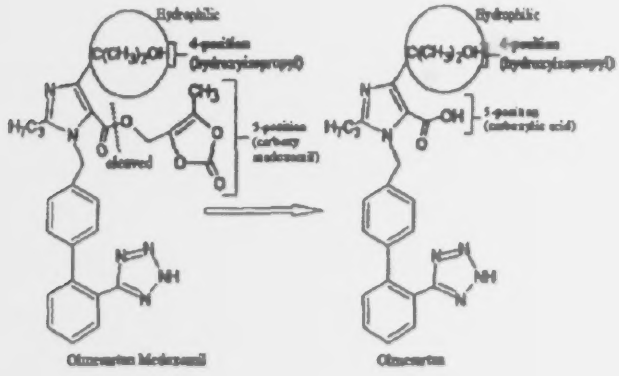


EXAMPLE 118

3. A regioisomer of another compound is one in which substituents around a ring are the same, but varied in position.

Appendix A

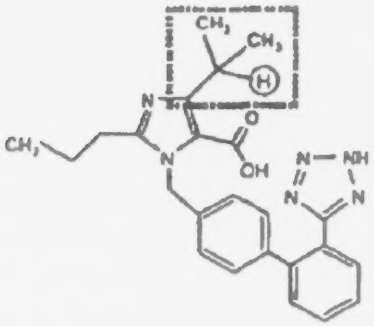
Olmesartan medoxomil also differs from losartan at the 5-position. Daiichi replaced losartan's hydroxymethyl group with a carboxy group masked by a medoxomil prodrug substituent to improve oral absorption. Like the hydroxymethyl group, the medoxomil moiety is metabolized to the carboxylic acid in the body. The structures of olmesartan medoxomil and olmesartan are depicted below.



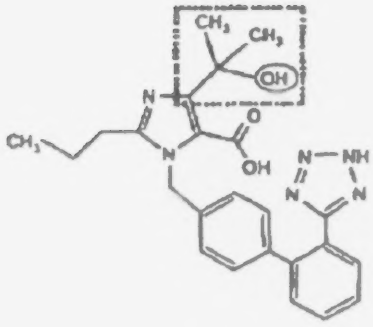
Other second-generation ARBs, all prior art to olmesartan medoxomil, include DuPont's DuP 532, in which losartan's chlorine at the 4-position is replaced with multiple lipophilic fluorine atoms ($-C_2F_5$), and six compounds disclosed in DuPont's U.S. Patent 5,137,902 ("the '902 patent"), each of which has a more lipophilic alkyl group at the 4-position. The ARBs disclosed in DuPont's '902 patent ("the '902 compounds" or "the '902 ARBs") are the closest structurally to olmesartan, with

Appendix A

Example 6 differing from olmesartan by only a single oxygen atom at the 4-position, as depicted below.



'902 Example 6



Olmesartan

Other second-generation ARBs differ more significantly from losartan by not containing an imidazole ring, including Merck & Co., Inc.'s L-158,809 compound, Ciba-Geigy Corp.'s valsartan, and Eisai Inc.'s E-4177 compound.

II.

Mylan filed multiple Abbreviated New Drug Applications ("ANDAs") with Paragraph IV certifications under the Hatch-Waxman Act, 21 U.S.C. § 355, challenging the '599 patent and seeking FDA approval to manufacture generic olmesartan medoxomil in various dosages and combinations. Daiichi responded by filing suit against Mylan for patent infringement in the United States District Court for the District of New Jersey. The parties stipulated to infringement of claim 13, leaving only Mylan's counterclaim that claim 13 would have been obvious in light of (1) the second-generation ARBs in DuPont's '902 patent, which Mylan alleged one of skill in the art would have been motivated to select as lead compounds; (2) Example 118, losartan's regioisomer, in DuPont's '069 patent, which Mylan alleged would have motivated one of skill in the art to modify the '902 compounds' lipophilic alkyl groups at the 4-position with olmesartan's hydrophilic hydroxyalkyl group; and (3) the well-known use of medoxomil as a prodrug.

After a ten-day bench trial, the district court held, in a comprehensive and well-reasoned opinion, that claim 13 of the '599 patent was not invalid as obvious.

Appendix A

Daiichi Sankyo Co., Ltd. v. Mylan Pharms. Inc., 670 F. Supp. 2d 359 (D.N.J. 2009). The court determined that Mylan had failed to show by clear and convincing evidence that one skilled in the art would have chosen the '902 ARBs as lead compounds over other better-studied ARBs with greater potency and thus had failed to establish a *prima facie* case of obviousness. *Id.* at 376-77. The district court went on to find that, even assuming that Mylan had shown the '902 ARBs to be leads, the structure of the '902 compounds differed significantly from olmesartan medoxomil, *id.* at 377-78, and that, even assuming structural similarity, Mylan had failed to prove that one of skill in the art would have been motivated to modify the 4- and 5-positions of the '902 ARBs to obtain olmesartan medoxomil, *id.* at 378-81. Regarding the 4-position, the court found that the emphasis on lipophilicity in both the '069 patent and the second-generation ARBs taught away from the use of a hydrophilic group at the 4-position and from any expectation that the use of a hydrophilic group would generate an ARB with significantly improved biological properties. *Id.* at 370-75, 378-80. Regarding the 5-position, the court found that converting olmesartan into a prodrug was a disfavored and unpredictable approach and that medoxomil was a disfavored prodrug. *Id.* at 380.

Finally, the district court concluded that even if Mylan had established a *prima facie* case of obviousness, secondary considerations counseled against a finding of obviousness. *Id.* at 381. Specifically, the court found evidence of unexpected results in olmesartan

medoxomil's enhanced potency and other favorable biological properties. *Id.* at 382-84. The court also found evidence of commercial success based on the significant market penetration of Benicar® despite being the seventh ARB on the market and despite Daiichi spending roughly the same amount in marketing as its competitors. *Id.* at 384-86.

On August 6, 2009, the district court entered final judgment and permanently enjoined Mylan's commercialization of olmesartan medoxomil until the expiration of the '599 patent. Mylan appealed. We have jurisdiction pursuant to 19 U.S.C. § 1295(a)(1).

DISCUSSION

Under the Patent Act, "[a] patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). While the ultimate determination of obviousness under § 103 is a question of law, it is based on several underlying factual findings, including (1) the scope and content of the prior art; (2) the level of ordinary skill in the pertinent art; (3) the differences between the claimed invention and the prior art; and (4) evidence of secondary factors, such as commercial success, long-felt need, and the failure of others. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966). After a bench trial, we review the district court's

conclusions of law *de novo* and findings of fact for clear error. *Golden Blount, Inc. v. Robert H. Peterson Co.*, 365 F.3d 1054, 1058 (Fed. Cir. 2004). A factual finding is clearly erroneous if, despite some supporting evidence, a reviewing court is left with the definite and firm conviction that a mistake has been made. *United States v. U.S. Gypsum Co.*, 333 U.S. 364, 395 (1948).

When a patent claims a chemical compound, a *prima facie* case of obviousness under the third *Graham* factor frequently turns on the structural similarities and differences between the compounds claimed and those in the prior art. *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (*en banc*) ("This court . . . reaffirms that structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness."); *see also Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1356-57 (Fed. Cir. 2008). Proof of obviousness based on structural similarity requires clear and convincing evidence that a medicinal chemist of ordinary skill would have been motivated to select and then to modify a prior art compound (*e.g.*, a lead compound) to arrive at a claimed compound with a reasonable expectation that the new compound would have similar or improved properties compared with the old. *Eisai*, 533 F.3d at 1357; *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007). In keeping with the flexible nature of the inquiry after *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007),

the motivation to select and modify a lead compound need not be explicit in the art. *Eisai*, 533 F.3d at 1357; *Takeda*, 492 F.3d at 1356-57.

Mylan challenges, as it must to prevail, every step in the district court's decision holding that Mylan failed to establish its *prima facie* case that olmesartan medoxomil would have been obvious in light of the prior art. Specifically, Mylan challenges the district court's finding that one of skill in the art would not have selected the six ARBs in DuPont's '902 patent as lead compounds, pointing to evidence that the '902 compounds are undisputedly the closest prior art. Mylan also challenges the court's finding that the '902 ARBs are not structurally similar to olmesartan medoxomil, arguing that one of the '902 compounds differs from olmesartan by only a single oxygen atom. Mylan also argues that the district court erred in finding no motivation to modify the '902 compounds at the 4- and 5-positions to arrive at olmesartan medoxomil when the '069 patent specifically taught a compound with a hydroxyalkyl group at the 4-position and the art taught medoxomil as a well-known prodrug for improving oral activity. Finally, Mylan contends that, contrary to the district court's finding, one of skill in the art would have had a reasonable expectation that modifying the '902 compounds to obtain olmesartan medoxomil would result in a similarly effective ARB.

In response, Daiichi defends the factual findings underlying the district court's determination that claim 13 of the '599 patent was not invalid as obvious. Daiichi

first argues that the district court correctly found that one of skill in the art would not have been motivated to select the '902 ARBs as lead compounds over other more potent and better-studied prior art ARBs. Daiichi next asserts that the district court correctly found no motivation to modify the '902 compounds to create olmesartan medoxomil based on the lack of structural similarity between the '902 ARBs and olmesartan medoxomil, the existence of thousands of possible modifications, the illogic of selecting the '902 compounds as leads only to reject their distinguishing characteristic of increased lipophilicity at the 4-position, the fact that the prior art taught away from such an alteration at the 4-position, and the unpredictability associated with the use of a prodrug in general and medoxomil in particular. Finally, according to Daiichi, the district court correctly found no reasonable expectation that the proposed modifications would lead to an ARB with significantly improved activity over losartan.

We agree with Daiichi that the district court did not err in holding that Mylan failed to establish a *prima facie* case of obviousness. Specifically, we agree that Mylan failed to show that one of ordinary skill in the art would have been motivated to select the '902 ARBs as lead compounds or, even if they had, that the skilled artisan would have been motivated to modify the '902 compounds to synthesize olmesartan medoxomil, the claimed invention. We address each in turn.

Appendix A

I. Selection of a Lead Compound

In rejecting the '902 ARBs as lead compounds, the district court accepted as true all of Mylan's evidence on the '902 compounds, including that they represented a continuation of DuPont's work on the ARBs disclosed in the '069 patent, including losartan, and thus could take advantage of the '069 patent's SAR data, and that the preferred '902 compounds "exhibit[ed] remarkable and unexpected potency as antihypertensives" with "oral antihypertensive activity approximately 2 to 4 fold higher than the most active compounds [of the '069 patent] which have been tested." *Daiichi Sankyo*, 670 F. Supp. 2d at 376 (alternations in original). Nevertheless, the court found that a medicinal chemist of ordinary skill would not have been motivated to select the '902 compounds over other second-generation ARBs, including L-158,809, DuP 532, the Eisai compounds, and valsartan, because many of the latter ARBs demonstrated greater potency and all had been more thoroughly studied than the '902 ARBs. Specifically, the court found that L-158,809 had 180 times, Example 7 of the Eisai compounds had 100 times, and DuP 532 had seven times the potency of losartan. *Id.* The court also found that while the '902 patent disclosed *in vivo* oral activity, the prior art included not only data on oral activity for all but the Eisai compounds, but also data on the binding affinity and intravenous activity for L-158,809, the Eisai compounds, DuP 532, and valsartan as well as selectivity data for L-158,809 and DuP 532. *Id.* Finally, the court found that DuP 532, which shared losartan's imidazole-biphenyltetrazole backbone, could

also benefit from the '069 patent's SAR data. *Id.* We see no clear error in the court's findings.

Mylan argues that because the '902 ARBs are undisputedly the closest prior art, that "should have been dispositive of the lead compound issue." Appellant Principal Br. 25. That argument runs contrary to our case law. In *Takeda*, we upheld a district court's finding that one of skill in the art would not have chosen the structurally closest prior art compound, compound b, as the lead compound in light of other compounds with more favorable characteristics. 492 F.3d at 1357-59. We reached the same result in *Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals, Inc.*, 471 F.3d 1369, 1377-79 (Fed. Cir. 2006). These cases illustrate that it is the possession of promising useful properties in a lead compound that motivates a chemist to make structurally similar compounds. Yet the attribution of a compound as a lead compound after the fact must avoid hindsight bias; it must look at the state of the art *at the time the invention was made* to find a motivation to select and then modify a lead compound to arrive at the claimed invention. *See Ortho McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008). Accordingly, proving a reason to select a compound as a lead compound depends on more than just structural similarity, but also knowledge in the art of the functional properties and limitations of the prior art compounds. *See Eli Lilly*, 471 F.3d at 1377-79. Potent and promising activity in the prior art trumps mere structural relationships.

Mylan further faults the district court for not following this court's "clarification that a 'lead compound' analysis does not require identification of a single, best, compound as a starting point" but "the prior art may point to more than a 'single lead compound for further development efforts.'" Appellant Principal Br. 24 (quoting *Altana Pharma AG v. Teva Pharms. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009)). But that misinterprets the district court's decision. As described above, the district court selected multiple compounds as leads, just not the compounds disclosed in the '902 patent. *Daiichi*, 670 F. Supp. 2d at 376. Contradicting itself, Mylan also faults the district court for selecting only five potential leads and for not including the '902 compounds among that finite number. While the lead compound analysis must, in keeping with *KSR*, not rigidly focus on the selection of a single, best lead compound, *see Altana Pharma*, 566 F.3d at 1008, the analysis still requires the challenger to demonstrate by clear and convincing evidence that one of ordinary skill in the art would have had a reason to select a proposed lead compound or compounds over other compounds in the prior art. Here, the district court did not commit error, let alone clear error, in finding that Mylan failed to meet that burden.

II. Motivation to Modify

The district court next found that, even accepting the '902 compounds as lead compounds, one of skill in the art would not have been motivated to modify the ARBs disclosed in the '902 patent to obtain olmesartan

medoxomil. Specifically, the court found that the prior art as a whole taught away from the use of a hydrophilic substitute at the 4-position of the imidazole ring, relying on, *inter alia*, the structural-activity relationship ("SAR") data in the '069 patent and the use of lipophilic groups at the 4-position in other second-generation compounds, including DuPont's '902 compounds. *Daiichi*, 670 F. Supp. 2d at 369-75. Accordingly, the district court also found that the prior art provided no motivation to modify the '902 compounds' lipophilic alkyls at the 4-position to the hydrophilic hydroxyisopropyl group of olmesartan. *Id.* at 378-80. Again we find no error in the district court's findings.

The '069 patent reveals a clear preference for lipophilic groups at the 4-position of the imidazole ring. The vast majority of the '069 compounds contain a lipophilic group at this position, as do twenty-seven of the thirty most active compounds, with two containing a neutral group and only one, Example 342, containing a hydrophilic group. J.A. 13717. This preference extends to the forty-two compounds in losartan's biphenyltetrazole series. Again, the vast majority, thirty-six out of forty-two compounds, have a lipophilic group at the 4-position and only four compounds, Examples 342, 329, 118, and 335, have a hydrophilic group. *Id.* at 7715. The few compounds with hydrophilic groups at the 4-position are drowned out by the sea of 4-lipophilic compounds, which are the essence of what the '069 patent teaches.

Three subseries analyses comparing the binding affinity of '069 patent compounds that vary only at the

imidazole ring's 4-position confirm the preference for lipophilicity at the 4-position. In the series of compounds with a biphenyltetrazole substitutent at the 1-position, a propyl group at the 2-position, and a hydroxymethyl group at the 5-position (1) three out of four compounds with a lipophilic group at the 4-position exhibit higher affinity binding, measured as a lower IC_{50}, than Example 334 with a neutral group, and (2) all four compounds with a lipophilic group exhibit higher affinity binding than Example 335 with a hydrophilic group. Specifically, Examples 124F, 124D, 124K, and 113 with lipophilic groups at the 4-position have IC_{50} values of 0.001 μM, 0.006 μM, 0.013 μM, and 0.020 μM, respectively, compared to an IC_{50} of 0.015 μM for Example 334, which has the highest binding affinity of any compound with a non-lipophilic group, and an IC_{50} of 0.26 μM for Example 335. *Id.* at 13721.

Similarly, in the series of compounds with a biphenyltetrazole substitutent at the 1-position, a propyl group at the 2-position, and a carboxylic acid at the 5-position, two out of three compounds with a lipophilic group at the 4-position exhibit higher affinity binding than Example 329 with a hydrophilic group. Specifically, Examples 265C (DuPont's DuP 532) and 251A have IC_{50} values of 0.003 μM and 0.045 μM compared to an IC_{50} of 0.076 for Example 329. *Id.* at 13720. Finally, Example 342, described above as the compound with the highest binding affinity of any compound with a hydrophilic group at the 4-position, has a lower binding affinity, higher IC_{50}, than Example 140J, which differs only by the substitution of a lipophilic group at the 4-position.

Id. at 13725. Thus, the compounds in the prior art, including the parties' proposed lead compounds, favor lipophilic 4-substitutents rather than the 4-hydrophilic group of olmesartan medoxomil.

An analysis of regioisomer pairs in which the 4- and 5-positions are transposed provides even further confirmation. For all eight regioisomer pairs, the regioisomer with a lipophilic group at the 4-position has higher binding affinity than the regioisomer with a hydrophilic group at that position. *Id.* at 13713-16. In the 6155 series, for example, two compounds with lipophilic chlorine atoms at the 4-position exhibit ten-fold and 100-fold better binding than compounds with a hydrophilic acetic acid or hydroxymethyl group, respectively. *Id.* at 13713. And in the biphenyltetrazole series, losartan with a chlorine at the 4-position has two-fold higher binding affinity than its regioisomer, Example 118, with a hydrophilic hydroxy-methyl group. *Id.* at 13716.

DuPont's second-generation ARBs repeat and enhance the preference for lipophilicity at the 4-position. Specifically, DuPont's DuP 532 replaces losartan's chlorine atom with a more lipophilic multiple fluorine group (-C2F5), and the six '902 compounds replace the chlorine with more lipophilic alkyl groups. No other second-generation ARB but olmesartan medoxomil has a hydrophilic group at the 4-position. *Id.* at 13722. Altogether, the '069 patent's SAR data and the structure of other second-generation ARBs counter any notion that one of skill in the art would have been motivated to

modify the '902 compounds' lipophilic alkyl groups to a hydrophilic group. Such a holding would have been based on hindsight.

Mylan argues that the motivation to modify comes directly from the '069 patent and specifically from Example 118, losartan's regioisomer, with its hydrophilic hydroxymethyl group at the 4-position. According to Mylan, the parties' experts agreed that Example 118 is one of the more potent and important of the compounds disclosed in the '069 patent, and thus, Mylan argues, although Example 118 is slightly less potent than losartan, it would have motivated one of skill in the art to alter the '902 compounds' alkyl groups to a hydrophilic group. Alternatively, Mylan argues, even without the benefit of Example 118, one of skill in the art would have been motivated to make the "minor" modification of hydroxylation of the '902 compounds' alkyls to produce a hydroxyisopropyl.[4] We disagree.

First, the SAR data in the '069 patent, described in detail above, contradict Mylan's arguments. Example 118 may be one of the more potent biphenyltetrazole compounds disclosed in the '069 patent, but it is one of only four to contain a hydrophilic group at the 4-position and one of only six to have a non-lipophilic group at that

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4. In fact, a difference of only a single oxygen atom between Example 6 of the '902 patent and olmesartan, as noted by Mylan, is of greater significance than it superficially appears, as it is the difference between functional groups, specifically an isopropyl and a hydroxyisopropyl.

position. Furthermore its regioisomer, losartan, displays greater binding affinity as do all the disclosed regioisomers with a lipophilic group compared to a hydrophilic group at the 4-position. And while the '069 patent's SAR data do not make available a subseries analysis for Example 118, all available subseries, as described above, demonstrate a clear preference for lipophilic groups over hydrophilic ones.

Second, Mylan's argument relies on first selecting the '902 compounds, which improved on losartan by using even more lipophilic alkyl groups at the 4-position, only to reject that very feature to obtain olmesartan medoxomil. *See Eisai*, 533 F.3d at 1358 (affirming a holding of non-obviousness based in part on a finding that the record "show[ed] no discernible reason for a skilled artisan to begin with lansoprazole only to drop the very feature . . . that gave [it an] advantageous property"). As the district court in this case put it, "a person of ordinary skill in the art would not select the '902 patent compounds as leads only to disregard one of their distinguishing characteristics, specifically their increased lipophilicity at the 4-position." *Daiichi*, 670 F. Supp. 2d at 379.

Finally, even crediting Mylan's argument that the '069 patent does not teach away from a hydrophilic group at the 4-position, the '069 patent simply does not provide a reason to make such a modification. We thus affirm the district court's decision holding that one of skill in the art would not have been motivated to modify the '902 compounds at the 4-position to obtain a compound with a hydrophilic hydroxyalkyl group.

Because we affirm the district court's findings that Mylan failed to establish either that one of skill in the art would have selected the '902 ARBs as leads or that one of skill in the art would have modified the '902 ARBs at the 4-position of the imidazole ring to obtain olmesartan medoxomil, we need not address the district court's alternative grounds for holding that Mylan failed to establish a *prima facie* case of obviousness or the court's findings on secondary considerations.

CONCLUSION

For the foregoing reasons, we affirm the district court's decision holding that claim 13 of the '599 patent was not shown to be invalid as obvious.

AFFIRMED

APPENDIX B — OPINION AND ORDER OF THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF NEW JERSEY

OPINION AND ORDER OF THE
UNITED STATES DISTRICT COURT FOR THE
DISTRICT OF NEW JERSEY

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

Civ. Nos. 06-3462, 07-3039, and 08-2752

DAIICHI SANKYO COMPANY, LIMITED
and DAIICHI SANKYO, INC.,

Plaintiffs and
Counterclaim Defendants,

v.

MYLAN PHARMACEUTICALS INC.,
MYLAN LABORATORIES INC., MATRIX
LABORATORIES, LTD., and MYLAN, INC.

Defendants and
Counterclaim Plaintiffs.

OPINION

HON. WILLIAM J. MARTINI

Appendix B

MARTINI, U.S.D.J.

Plaintiffs Daiichi Sankyo Company, Limited and Daiichi Sankyo, Inc. (collectively "Daiichi Sankyo") are the inventors and producers of olmesartan medoxomil, the active ingredient in the hypertension medications Benicar, Benicar HCT, and Azor. Defendants Mylan Pharmaceuticals Inc., Mylan Laboratories Inc., Matrix Laboratories, LTD., and Mylan, Inc. (collectively "Mylan") are drug manufacturers seeking to market a generic version of olmesartan medoxomil. Daiichi Sankyo filed this suit claiming infringement of its United States Patent No. 5,616,599 ("the '599 patent"). Mylan concedes infringement of the '599 patent, but counters that the '599 is invalid due to obviousness. Claim 13 of the '599 patent is the only claim at issue.[1]

The parties tried this case before the Court on various days from March 31, 2009 to April 20, 2009. Thereafter, they submitted proposed findings of fact and conclusions of law. The Court carefully considered the parties' submission and the record evidence. For the reasons set forth below,[2] the Court finds that Mylan

1. Initially, Daiichi Sankyo claimed that Mylan infringed on Claim 9 and Claim 13 of the '599 Patent. Claim 9 covered the chemical compound olmesartan. (SF ¶ 9.) Daiichi Sankyo has withdrawn any claim that Mylan infringes Claim 9 and has executed a covenant not to sue Mylan on Claim 9 for future products.

2. This Opinion shall constitute the Court's findings of fact and conclusions of law pursuant to Fed. R. Civ. P. 52(a).

has failed to prove by clear and convincing evidence that the '599 patent is obvious under 35 U.S.C. § 103(a). As a result, the '599 patent is neither invalid nor unenforceable. Mylan has infringed on the '599 patent under 35 U.S.C. § 271(e)(2).

I. BACKGROUND

Olmesartan medoxomil is the active ingredient in several medications produced by Daiichi Sankyo used for the treatment of hypertension. (Stipulation of Fact ("SF") ¶ 13.) Hypertension, or high blood pressure, is one of the world's leading causes of death. (Brown 4/2/09 Tr. JA 282:20-22.) Approximately seventy-three million people in the United States age twenty and older suffer from high blood pressure, with roughly sixty-two percent of this group receiving treatment. (Boghigian 4/8/09 Tr. JA 873:9-18; JA 5275.) Hypertension contributes to stroke, myocardial infarction, and other life-threatening conditions. (Brown 4/2/09 Tr. JA 282:6-10; Carey 4/14/09 Tr. JA 1009:5-9.)

A. The Renin-Angiotensin System and Early Angiotensin Receptor Blockers

Starting in the 1970s, scientists began to understand the role of the renin-angiotensin system ("RAS") in controlling hypertension. (Brown 4/2/09 Tr. JA 279:1-JA 281:21; DTX 356-B, at JA 5175-81, 5171 & 5197-200.) Angiotensin II, a peptide produced by the RAS, binds to AT_1 receptors, which are found on the surfaces of a variety of cell types including blood vessels and renal

tubules. (*Id.*) The constriction caused by the binding of the angiotensin II to the AT_1 receptors leads to increased blood pressure. (*Id.*)

By the late 1970s, scientists developed angiotensin converting enzyme inhibitors ("ACE" inhibitors), which directly interfered with the production of angiotensin II. (Brown 4/2/09 Tr. JA 282:22-284:5.) While ACE inhibitors proved effective, these compounds resulted in certain unwanted side-effects. (Cohn 4/7/09 Tr. JA 784:11-JA 785:23.)

In 1982, a Japanese pharmaceutical company, Takeda Chemical Industries Ltd. ("Takeda"), developed the first non-peptide compounds, which blocked the binding of angiotensin II to AT_1 receptors. (Brown 4/2/09 Tr. JA 284:10-285:16; Weinstock 3/31/09 Tr. JA 96:14-97:10.) Termed angiotensin II receptor blockers ("ARBs"), these Takeda compounds contained an imidazole ring—a five membered ring having two nitrogen atoms. (Weinstock 3/31/09 Tr. JA 101:4-102:7; DTX 125, at JA 4164.) One early Takeda compound, known as S-8307, employed a single six-membered phenyl ring through a methylene linkage (CH_2) at the 1-position of the imidazole ring, a butyl group at the 2-position, a chlorine atom (Cl) at the 4-position, and an acetic acid (CH_2COOH) at the 5-position. (Weinstock 3/31/09 Tr. JA 102:10-20, 104:10-106:3; DTX 356-A, at JA 5127, 5130-32.)

Appendix B

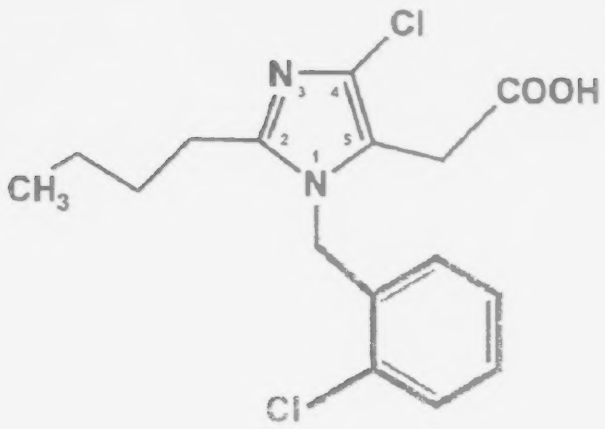

Figure 1 Chemical Structure of S-8307.
(DTX 356-A, at JA 5132.)

Although the first of its kind, the Takeda compounds exhibited limited therapeutic value due to a lack of oral activity. (Weinstock 3/31/09 Tr. JA 100:7-8.)

B. Losartan

Using Takeda's work as lead, E.I. du Pont de Nemours Company, Inc. ("DuPont") embarked on its own ARB development program in 1982. (*Id.* at JA 95:23-96:1.) Several years later, in 1989, DuPont announced that it had selected one of its compounds, DuP 753, also known as losartan, for clinical trials. (*Id.* at JA 111:5-9.)

Appendix B

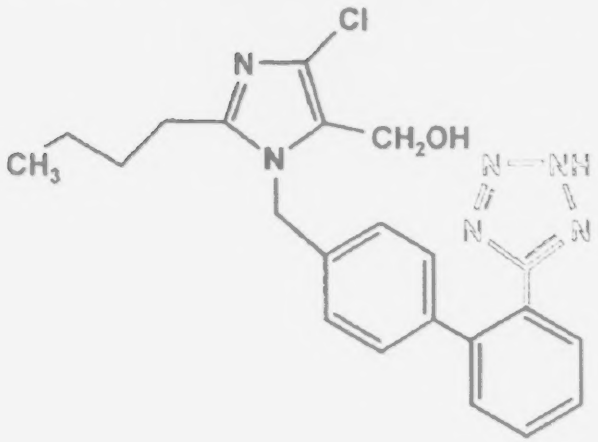

Figure 2 Chemical Structure of Losartan.
(DTX 356-A, at JA 5138.)

Losartan resembled Takeda S-8307 in the sense that it retained the imidazole ring and the chlorine atom at the 4-position of the imidazole ring. The compound, however, differed through the addition of a biphenyl tetrazole—a six membered phenyl and a tetrazole—at the 1-position of the imidazole ring, as well as a hydroxymethyl at the 5-position. (DTX 356-A, at JA 5132, 5138.)

As a result of these changes, losartan exhibited a ten-fold greater binding affinity[3] and twenty-fold greater oral activity over the Takeda compounds. (Weinstock 03/31/09 Tr. JA 112:19-JA 113:8.) Losartan represented

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3. Binding affinity is measured as an IC_{50}, which is the concentration of a compound that inhibits 50% of the binding of angiotensin II to the receptor. (Weinstock 3/31/09 Tr. JA 98:1118.)

a "milestone," becoming the first non-peptide ARB clinical candidate. (*Id.* at JA 111:5-9; PTX 190, at JA 10028.) DuPont disclosed losartan and several hundred structurally related ARB compounds in United States Patent No. 5,138,069 ("the '069 patent"). (Weinstock 3/31/09 Tr. JA 119:11-23; DTX 195, at JA 3602-746.)

C. Development of Olmesartan Medoxomil

Following DuPont's success with losartan, more than twenty pharmaceutical companies established ARB research programs. (Lipinski 4/20/09 Tr. JA 1558:19-20.) Daiichi Sankyo started its own program, in late 1989, using losartan as a reference. (Yanagisawa 4/17/09 Tr. JA 1424:10-12, 1457:1-5.) The company employed a team of scientists lead by Dr. Hiroaki Yanagisawa "to come up with a drug that had ten times the activity of losartan" with "long enough duration so as to be dosed once-a-day." (*Id.* at JA 1422:10-20.)

After testing several hundred compounds, Daiichi Sankyo discovered the chemical compound olmesartan. (*Id.* at JA 1447:5-6; PTX 202-A, at JA 10499, 10256-498.) Dissatisfied with the compound's oral absorption, Daiichi Sankyo attempted to improve olmesartan's properties by attaching various ester promoieties to the chemical, converting olmesartan into the prodrug olmesartan medoxomil. (Yanagisawa 4/17/09 Tr. JA 1442:25-1446:1; PTX 26, at JA 9548-63.) The company discovered that a medoxomil ester at the 5-position of the imidazole ring led to a compound with 100 times the potency of losartan on oral administration. The

medoxomil ester also crystallized, an "important factor in [a drug's] manufacturing, its formulation and in quality assurance." (Yanagisawa 4/17/09 Tr. JA 1445:20-23.)

Based on this research, on April 26, 1991, Daiichi Sankyo filed a patent application in Japan, and subsequently in the United States, claiming olmesartan and olmesartan medoxomil. (SF ¶ 8; PTX 1, at JA 5611.) This led to the issuance the '599 patent by the United States Patent and Trademark Office ("PTO") on April 1, 1997, with Claim 13 specifically covering olmesartan medoxomil.[4] (SF ¶¶ 6, 11; PTX 1, at JA 5610.)

Like losartan and the early Takeda compounds, olmesartan medoxomil retained an imidazole backbone and possessed a biphenyl tetrazole at the 1-position of the imidazole ring. (PTX 1, JA 5610-11.)

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4. The '599 Patent is entitled "Angiotensin II Antagonist 1-Biphenylmethylimidazole Compounds And Their Therapeutic Use." (SF ¶ 6.) The chemical name of olmesartan medoxomil is (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1-{4-[2-(tetrazole-5-yl)phenyl]phenyl}methylimidazole-5-carboxylate. (SF ¶ 12.)

Appendix B

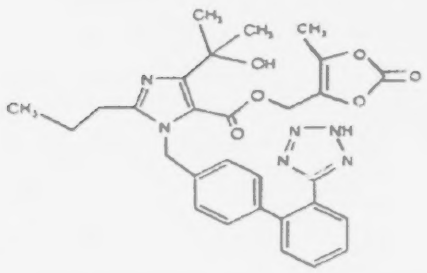

Figure 3 Chemical Structure of Olmesartan Medoxomil. (DTX 356-A, at JA 5145.)

However, olmesartan medoxomil differed from losartan in two major respects. First, at the 4-position of the imidazole ring, olmesartan medoxomil employed a hydroxyisopropyl ($C(CH_3)_2OH$) instead of a chlorine atom. (Weinstock 3/31/09 Tr. JA 121:11-17, 125:6-127:1 & 129:3-5; DTX 356-A, at JA 5143, 5146.) Second, the compound contained a medoxomil ester linked to a carboxylic acid at the 5-position.[5] (Weinstock 3/31/09 Tr. JA 121:1-10; DTX 356-A, at JA 5143, 5146.)

D. DuPont's '902 Patent Compounds and DuP 532

DuPont itself continued to look for improvements to losartan prior to Daiichi Sankyo's April 26, 1991 patent application in Japan. (Hieble 4/7/09 Tr. JA 711:17-23.) This additional research led to the disclosure of the '902 patent compounds, as well as DuP 532.

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5. *In vivo*, enzymes cleave medoxomil from olmesartan medoxomil, liberating olmesartan (Weinstock 3/31/09 Tr. JA 123:3-17; DTX 356-A, at JA 5145.) Instead of medoxomil at the 5-position, olmesartan possesses a carboxylic acid (COOH). (*Id.*)

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Following the disclosure of the '069 patent compounds, DuPont revealed six additional compounds in United States Patent No. 5,137,902 ("the '902 patent") with a February 4, 1991 priority date. (DTX 96, at JA 3747-52.) A "culmination of DuPont's ARB research," the '902 patent compounds utilized losartan's biphenyl-tetrazole-imidazole structure and contained a straight-chain propyl at the 2-position of the imidazole ring. (Weinstock 3/31/09 Tr. JA 119:24-120:12; DTX 96, at JA 3748.) Examples 1, 2, and 6 of the '902 patent compounds use a carboxylic acid at the 5-position, while Examples 3, 4, and 5 employ an aldehyde (CHO). (Lipinski 4/20/09 Tr. JA 1616:1-2.) At the 4-position of the imidazole ring, the '902 patent compounds contain various branched alkyls, including an ethyl, methyl, t-butyl, and isopropyl. (DTX 356-A, at JA 5143.)

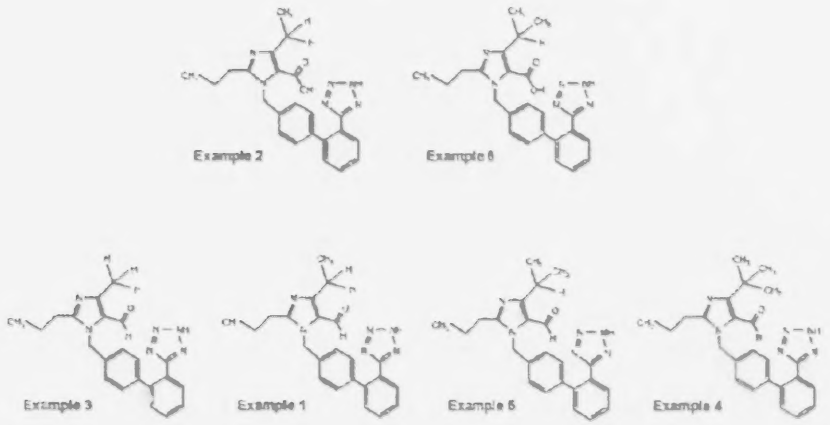

Figure 4 Chemical Structures of the '902 patent compounds. (DTX 356-A, at JA 5143.)

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Although DuPont ultimately chose not to commercialize the '902 patent compounds, the most preferred '902 patent compounds exhibited oral activity "approximately 2 to 4 fold higher than most active compound specifically disclosed [in the '069 patent] which have been tested." (Brown 4/2/09 Tr. JA 405:14-16; DTX 96, at JA 3748.)

In mid-April 1991, DuPont also reported DuP 532, as part of its "new series of 4perfluoro-alkylimidazole." (PTX 244, at JA 10761-762; PTX 246, at JA 10765-766; Weinstock 4/6/09 Tr. JA 517:3-22; Timmermans 4/16/09 Tr. JA 1383:13-1384:16; Lipinski 4/20/09 Tr. JA 1573:24-1575:3, 1576:24-1577:15.) DuPont used losartan's biphenyl-tetrazole-imidazole structure for DuP 532, but changed the 4-position of losartan from a chlorine atom to a substituent containing multiple fluorine atoms (CF_2CF_3). (Weinstock 4/1/09 Tr. JA 213:3-6; 4/6/09 Tr. JA 517:19-22.) Unlike losartan's hydroxymethyl at the 5-position, DuP 532 employed a carboxylic acid (COOH). (Weinstock 3/31/09 Tr. JA 115:2-14; DTX 356-A at JA 5138, 5140.)

Appendix B

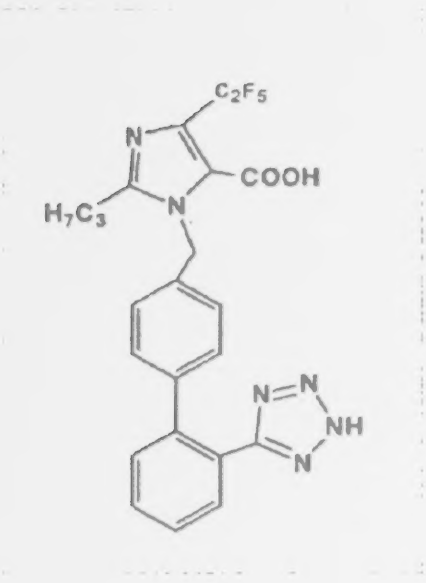

Figure 5 Chemical Structure of DuP 532.
(PTX 175, at JA 9907.)

Through these changes, DuPont improved upon the oral activity of losartan. DuP 532 exhibited a three-fold increase in oral activity when compared to the company's breakthrough drug. (Timmermans 4/16/09 Tr. JA 391:12-16; Lipinski 4/20/09 Tr. JA 1577:11-15.)

E. Other "Second Generation" ARBs

Daiichi Sankyo and DuPont were not alone in their respective quests to develop compounds superior to losartan. By April 1991, several other large pharmaceutical companies contemporaneously

developed their own "second generation" ARBs. Merck & Co. ("Merck") revealed L-158,809. Ciba-Geigy, Ltd. ("Ciba-Geigy") developed valsartan. Eisai Co. Ltd. ("Eisai") released information about a series of compounds, including E-4177 and Takeda disclosed candesartan cilexetil. (Weinstock 3/31/09 Tr. JA 48:6-9, 50:21-51:10, 62:2-5 & 63:1.)

The structure of these "second generation" ARBs differed from the early Takeda compounds, losartan, and olmesartan medoxomil. Several of these drugs did not utilize an imidazole ring: L-158,809 and E-4177 used an imidazopyridine ring, candesartan cilexetil employed a benzimidazole ring, and valsartan lacked any ring whatsoever. (PTX 248, at JA 10769-770, PTX 250, at JA 10773-813.) These compounds also differed at the position corresponding to the 2-position of the imidazole ring: E-4177 utilized a hydrocarbon ring, while cyclopropyl and candesartan cilexetil contained a non-hydrocarbon carbon chain ethyoxy. (DTX 99, at JA 3753-94; PTX 250, at JA 10773813.)

F. Commercialization of Olmesartan Medoxomil and Other ARBs

As a result of this extensive pharmaceutical research, seven ARBs have been released for public consumption. (Boghigian 4/8/09 Tr. JA 873:25-874:2.) Daiichi Sankyo commercialized olmesartan medoxomil in three products, specifically Benicar and two

combination drugs Benicar HCT and Azor.[6] (SF ¶¶ 17-19.) At the time of Benicar's launch in 2002, six other ARBs in the drug's class had hit the market. (Boghigian 04/8/09 Tr. JA 874:11-12.) The oldest drug, Cozaar (losartan), manufactured by DuPont and then Merck, had been available for seven years, while the newest drug Teveten, manufactured by Abbott Laboratories, had been on the market for roughly two years. (PTX 584, at JA 25089.)

In its first year, Benicar enjoyed $22.5 million in gross sales. (PTX 590-1, at JA 25092.) By 2008, the combined gross sales of Benicar, Benicar HCT, and Azor reached $1.3 billion. (*Id.*) During the same time, Benicar's market share grew to 16.6%, making it the third largest ARB on the market. (PTX 583, at JA 25088.)

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6. On April 25, 2002, the FDA approved the sale of Benicar tablets (5mg, 20mg, and 40mg), which contain the active ingredient olmesartan medoxomil, for the treatment of hypertension. (SF ¶¶ 17.) Daiichi Sankyo also received New Drug Applications ("NDA") for the sale of Benicar HCT and Azor tablets on June 5, 2003 and September 26, 2007 respectively. (*Id.* ¶¶ 18-19.) Benicar HCT is a drug containing the active pharmaceutical ingredients olmesartan medoxomil and hydrochlorothiazide (HCTZ) and Azor is a drug containing the active phamaceutical ingredients olmesartan medoxomil and amlodipine besylate. (*Id.* ¶ 18.)

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G. Mylan's Abbreviated New Drug Applications and the Current Litigation

Following Daiichi Sankyo's success with Benicar and the combination drugs, Mylan submitted several Abbreviated New Drug Applications ("ANDA"), seeking approval to manufacture and sell generic versions of Benicar, Benicar HCT, and Azor. (SF ¶¶ 21-23.) In conjunction with each ANDA, Mylan filed a certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV), commonly referred to as a "Paragraph IV certification." (*Id.* ¶ 24.) These certifications stated that, in Mylan's "opinion and to the best of [their] knowledge, [the '599 patent is] invalid, unenforceable or will not be infringed by the manufacture, use, sale, offer for sale, or importation of [Mylan's ANDA products]." (*Id.*)

After filing each Paragraph IV certification, Mylan sent a Paragraph IV Notice Letter to Daiichi Sankyo alleging that Mylan's ANDA products will not infringe any valid claim of the '599 patent. (*Id.* ¶ 25.) Each Notice Letter affirmed that Mylan provided the factual and legal bases, known by the company at that time, that no valid claim of the '599 patent would be infringed, either literally or under the doctrine of equivalents, by the commercial manufacture, use, or sale of Mylan's ANDA products prior to the expiration of the '599 patent. (*Id.*)

After receiving Notice Letters for Benicar, Benicar HCT, and Azor, Daiichi Sankyo filed three separate actions against Mylan, each within the relevant 45-day statutory time period. (*Id.* ¶ 25.) These actions have been consolidated for all purposes under the present matter. (*Id.* ¶ 26.)

Appendix B

II. JURISDICTION, VENUE, AND APPLICABLE LAW

This Court has subject matter jurisdiction over Daiichi Sankyo's patent infringement claims and Mylan's counterclaims pursuant to 28 U.S.C. §§ 1331 and 1338(a). Since this action arises under the patent laws of the United States, the Court must apply the precedents of the United States Court of Appeals for the Federal Circuit, which has jurisdiction over any appeal of this judgment. *See* 28 U.S.C. § 1295(a).

III. CONCLUSIONS OF LAW

A. Standard for Obviousness

Under the United States Patent Act, an invention cannot be patented if "the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a). Since patents are presumed to be valid, *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 968 (Fed. Cir. 2006), the party seeking to invalidate a patent based on obviousness must demonstrate "by clear and convincing evidence that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). Clear and convincing evidence places in the fact finder "an abiding conviction

that the truth of [the] factual contentions are 'highly probable.'" *Colorado v. New Mexico*, 467 U.S. 310, 316 (1984) (citation omitted).

The obviousness determination turns on underlying factual inquiries involving: (1) the scope and content of the prior art, (2) the level of ordinary skill in the art, (3) the differences between the claimed invention and the prior art, and (4) secondary considerations, such as commercial success and satisfaction of a long felt need. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

In cases involving chemical compounds, the patent challenger may establish a prima facie case of obviousness if the party "identifies] some reason that would have led a chemist to modify a known compound in a particular manner. . . ." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007). If a patent challenger makes a prima facie showing of obviousness, the patent owner may rebut based on "unexpected results" by demonstrating "that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995).

B. Level of Ordinary Skill in the Art

The Court must first determine the level of ordinary skill in the art at the time of the filing of the '599 patent. Obviousness is judged from the perspective of a

hypothetical person of ordinary skill in the art. *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138 (Fed. Cir. 1985). The hypothetical person must be viewed as an "inventor working in his [or her] shop with the prior art references—which he [or she] is presumed to know—hanging on the walls around him [or her]." *Union Carbide Corp. v. Am. Can Co.*, 724 F.2d 1567, 1567 (Fed. Cir. 1984). Such an individual possesses "ordinary creativity" and is not "an automaton." *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420-21 (2007). In cases where the level of skill is high, courts may "assume a keener appreciation of the nuances taught by the prior art." *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1351 (Fed. Cir. 2001).

Here, the pertinent field of art is the design, development, synthesis, and testing of ARBs prior to the priority date of the '599 patent, April 26, 1991. (Weinstock 3/31/09 Tr. JA 124:7-125:5.) The parties agree that a person of ordinary skill is an experienced medicinal chemist[7] with the ability to analyze structure-activity relationships ("SAR").[8] (*Id.*) Not only would a person of ordinary skill possess the ability to design,

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7. Medicinal chemistry is a multi-disciplinary field concerned with the design, development, synthesis, and testing of biologically active compounds that involves aspects of organic chemistry, biological, medical, and pharmaceutical sciences. (Weinstock 3/31/09 Tr. JA 74:2-3.)

8. A structure activity relationship is the correlation of a systematic structural change with the resulting change in the compound's activity. (*Id.* at JA 88:20-89:16.)

evaluate, and synthesize compounds, but such an individual would be able to evaluate pharmacological data obtained from routine screening assays. (*Id.* at JA 124:7-21.)

C. Scope and Content of the Prior Art

1. *The Prior Art at the Time of the Filing of the '599 Patent*

Under *Graham*, the Court must next define the scope and content of the prior art as of April 26, 1991. Prior art is limited to "analogous" references "from the same field or endeavor" or, if not, from the same field or endeavor art that is "reasonably pertinent to the particular problem with which the inventor is involved." *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004). "When the references are all in the same or analogous fields, knowledge thereof by the hypothetical person of ordinary skill is presumed . . . and the test is whether the teachings of the prior art, taken as a whole, would have made obvious the claimed invention." *In re Gorman*, 933 F.2d 982, 986 (Fed. Cir. 1991) (citation omitted).

In the instant matter, the prior art includes DuPont's '069 patent and '902 patent, as well as the thirteen scientific publications documenting DuPont's work. The prior art also incorporates the various compounds disclosed in the '069 and '902 patents, which share olmesartan medoxomil's chemical "backbone"—an imidazole ring with a biphenyl tetrazole at the 1-

position and a straight chain alkyl at the 2-position. Additionally, the prior art encompasses patents related to other second generation ARB compounds published before April 26, 1991, such as Merck's L-158,809, compounds disclosed by Eisai on April 13, 1991 in patent EP 0 420 237 B1 (the "Eisai compounds"), candesartan cilexetil, and valsartan. (PTX 247, at JA 10767-768; PTX 250, at JA 10773-813; DTX 99, at JA 03753-794; PTX 204, at JA 10500-532.)

2. *Whether the Prior Art "Taught Away" From the Use of a Hydrophilic Substituent*

The parties disagree as to whether the prior art, as a whole, "taught away" from the use of a hydrophilic, as opposed to lipophilic, substituent at the 4-position of the imidazole ring.[9] Whether prior art teaches away or toward a claimed invention is a finding of fact that is a "subsidiary requirement" of the "scope and content of the prior art." *Ortho-McNeil Pharm., Inc. v. Kali Labs., Inc.*, 482 F. Supp. 2d 478, 516 (D.N.J. 2007) (citing *DyStar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1360 (Fed. Cir. 2006)). When the prior art "teaches away" from a particular combination of known elements, the successful combination of those elements is less likely to be obvious. *E.I. Du Pont de Nemours & Co. v. MacDermid, Inc.*, Civ. No. 06-3383, 2008 WL 4952450, at *26 (D.N.J. Nov. 19, 2008) (citing *KSR Int'l Co.*, 550 U.S. at 1740).

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9. Hydrophilicity refers to a substituent's tendency to be solvated by water, and lipophilic refers to a molecule's affinity for a fat-like environment. (Weinstock 4/1/09 Tr. JA 205:6-12)

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Under relevant Federal Circuit precedent, the prior art "teaches away" if a person having ordinary skill, "upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). For a reference to teach away, it must state more than a general preference for an alternative invention. It must "criticize, discredit, or otherwise discourage" investigation into the invention claimed. *In re Fulton*, 391 F.3d 1195, 1201 (Fed. Cir. 2004).

In light of the above standard, the Court finds that the prior art taught away from the use of a hydrophilic group at the 4-position of the imidazole ring. The prior art evidences more than a general preference for the use of a lipophilic substituent at the 4-position, clearly discouraging a person of ordinary skill from using a hydrophilic group at this position. This clear discouragement is established by the overwhelming weight of the art, specifically language found in the '069 patent, the emphasis on lipophilicity at the 4-position in DuPont's second generation ARB compounds, DuPont SAR data from the '069 patent, and the use of lipophilic substituents at the 4-position in other second generation compounds.

a. Language Found in the '069 Patent

The '069 patent, itself, contains language which would discourage a person of ordinary skill from using a hydrophilic substituent at the 4-position of the

imidazole ring. The '069 patent expresses a preference for a lipophilic group at the 4-position as demonstrated by a regioisomer comparison.[10] The '069 patent states that: "[i]n all series examined, the more rapidly eluted isomer of a given pair has greater biological potency then the less rapidly eluted isomer." (PTX 195, at JA 10093.) The patent goes on to define the "more rapidly eluted isomer" as a compound with an imidazole ring containing a lipophilic chlorine atom at the 4-position of the imidazole ring, and the "less rapidly eluted isomer" as a compound with a hydroxymethyl (CH_2OH) at the 4-position. (*Id.*) Of the over 400 compounds released in the '069 patent, the hydroxymethyl referenced in this statement is one of the most hydrophilic. (Timmermans 4/16/09 Tr. JA 1366:24-1367:1; Weinstock 4/1/09 Tr. JA 185:17-25.) The compound containing the hydroxymethyl also has the least potency as compared to losartan. (Weinstock 4/1/09 Tr. JA 185:17-25.) Based on this statement alone, a person of ordinary skill in the art, upon reading this language, would have been discouraged from using a hydrophilic group at the 4-position.[11]

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10. Regioisomers are two compounds that differ in the arrangement of substituents. For purposes of the '069 patent compounds, following a chemical reaction, regioisomers formed with differing 4- and 5-positions of the imidazole ring. (Timmermans 4/16/09 Tr. JA 1338:23-1339:4.)

11. Daiichi Sankyo also points to statements found in a non-prior art reference written by the inventors of losartan David Carini et al., titled "Nonpeptide Angiotensin II Receptor Antagonists: The Discovery of a Series of N-(Biphenylylmethyl) imidazoles as Potent, Orally Active Antihypertensives" ("Carini

(Cont'd)

b. Lipophilicity in DuPont's Second Generation Compounds

The preference for a lipophilic substituent at the imidazole ring's 4-position is further demonstrated by DuPont's second generation ARB development. Following DuPont's success with losartan, the company engaged in additional research to create an improved

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(Cont'd)
Article"), as evidence of an explicit statement that discourages the use of a hydrophilic substituent at the 4-position of the imidazole ring. (Weinstock 4/6/09 Tr. JA 526:17-21, DTX 122 JA 4136-162.) This article was published several months after the relevant priority date. As stated above, a "reference" teaches away "when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 27 F.3d at 553. Under the standard for obviousness, a person of ordinary skill is presumed to have knowledge of all prior art references. *In re Gorman*, 933 F.2d at 986. A reference qualifies as prior art if it was published before the priority date. *See* 35 U.S.C. 102(a). Turning to the facts at hand, the Carini Article fails to qualify as a prior art reference. The relevant priority date is April 26, 1991. The article was published in August 1991, several months after this date. Even though the Carini Article explicitly states that, in the biphenyl tetrazole series, disclosed in the '069 patent, "[a] large lipophilic and electron-withdrawing substituent seems to be favored" and "[t]he 4-position best tolerates a large, electronegative, lipophilic substituent," the Court cannot and need not consider this publication for purposes of its teaching away analysis. (DTX 122, at JA 4144, 4150.)

antihypertensive. (Lipinski 4/20/09 Tr. JA 1559:8-13; Weinstock 4/6/09 Tr. JA 517:3-22.) As a result of this research, DuPont developed two second generation ARBs—DuP 532 and the '902 patent compounds. These second generation compounds not only shared losartan's structural backbone, but also enhanced losartan's antihypertensive properties by increasing lipophilicity at the 4-position of the imidazole ring. (Lipinski 4/20/09 Tr. JA 1559:2-7, 1677:18-20.)

DuP 532 and the '902 patent compounds modified the chlorine atom at the 4-position of the imidazole ring in favor of more lipophilic compounds. (Weinstock 4/1/09 Tr. JA 213:3-6, 216:8-10.) DuP 532 employed a more lipophilic substituent containing multiple fluorine atoms (CF2CF3), while the '902 patent compounds contained a series of more lipophilic alkyl substituents, including methyl, ethyl, isopropyl, and t-butyl. (*Id.*)

Based on these changes, DuP 532 and the '902 patent compounds exhibited better antihypertensive activity than losartan. (Lipinski 4/20/09 Tr. JA 1577:11-15.) By making the 4-position more lipophilic, DuP 532 generated a three-fold increase in oral activity over losartan. (Timmermans 4/16/09 Tr. JA 1391:12-16; Lipinski 4/20/09 Tr. JA 1577:11-15.) The most preferred compounds in the '902 patent—Examples 1, 2, and 4—exhibited "oral antihypertensive activity approximately 2 to 4 fold higher than the most active compounds specifically disclosed [in the '069 patent] which have been tested." (DTX 96, at JA 3748.)

At trial, both parties' medicinal chemistry experts emphasized the importance of lipophilic type binding forces in the '902 patent compounds. Mylan's medicinal chemistry expert, Dr. Joseph Weinstock, acknowledged that "lipophilicity is . . . an important part of this patent." (Weinstock 4/1/09 Tr. JA 218:19.) He further agreed that:

> the '902 patent teaches that a lipophilic but not an electron-withdrawing group, at the 4-position of the imidazole gives compounds with potent binding activity and are orally active . . . [which] . . . emphasizes the importance of lipophilic-type binding forces between the surface of the antagonist and the receptor.

(*Id.* at JA 218:12-15, 220:1-3.) Likewise Daiichi Sankyo's expert in medicinal chemistry, Dr. Christopher Lipinski, opined that "the '902 patent confirms the preference for lipophilic groups at the 4-position." (Lipinski 4/20/09 Tr. JA 1559:14-16.)

b. DuPont's SAR from the '069 Patent

DuPont's SAR from the '069 patent also evidences a preference for lipophilic substituents at the 4-position of the imidazole ring. This data confirms that lipophilic substituents at the 4-position exhibited the best binding affinity. The '069 patent disclosed the specific binding affinity data for over 200 compounds. (Weinstock 3/31/09 Tr. JA 119:19-20; PTX 195, at JA 10213-215.) The vast majority of the '069 patent compounds contains lipophilic substituents at the 4-position. (Lipinski

4/20/09 Tr. JA 1555:8-10.) Of the forty-two compounds tested with a biphenyl tetrazole structure, thirty-six have lipophilic substituents at the 4-position, four use hydrophilic substituents, and two contain a neutral substituent. (*Id.* at JA 1649:7-1650:21.)

A subseries analysis of lipophilic and non-lipophilic compounds from the '069 patent illustrates a preference for lipophilicity. By looking at compounds with identical 1-, 2-, and 5-positions and varied 4-positions, Dr. Lipinski and Daiichi Sankyo's second medicinal chemistry expert Dr. Pieter Timmermans concluded that the advantage of lipophilicity is evidenced across all subseries, including non-biphenyl tetrazole series. (Timmermans 4/16/09 Tr. JA 1376:9-22, 4/17/09 JA 1530:3-6; Lipinski 4/20/09 Tr. JA 1556:18-21.) As stated by Dr. Timmermans, a comparison amongst subseries taught that a medicinal chemist could "make very potent molecules if you put a large lipophilic group on the 4-position compared to neutral, perhaps or more importantly, hydrophilic groups." (Timmermans 4/16/09 Tr. JA 1376:9-22.)

In rebuttal, Mylan points to six compounds in the '069 patent with high binding affinities and neutral or hydrophilic groups at the 4-position. (Weinstock 4/1/09 Tr. JA 233:13-17.) Mylan argues that these compounds, which equal roughly 1% of the disclosed compounds in the '069 patent, suggest the use of a hydrophilic group at the 4-position, because two of these compounds

exhibited binding affinities that exceeded losartan.[12] (Lipinski 4/20/09 Tr. JA 1651:2-9; DTX 256-A at JA 5157, 415-C at JA 5298.)

However, a placement of these six compounds in their respective subseries confirms the importance of lipophilicity for best binding activity. For each non-lipophilic compound highlighted by Mylan, the '069 patent provides a comparable compound with identical 1-, 2-, and 5-positions but with a lipophilic group at the 4-position. (PTX 628-2, at JA 25115.) In each instance, the compound containing a lipophilic 4-position exhibited better binding activity. (Weinstock 4/1/09 Tr. JA 260:13-19.)

This same emphasis is highlighted by a comparison of regioisomer pairs in the '069 patent. As both parties' experts agreed, an analysis of paired compounds, or "regioisomer" pairs, with two positions switched gives helpful information about the SAR at these positions. (Weinstock 4/6/09 Tr. JA 510:24-511:6; Lipinski 4/20/09 Tr. JA 1557:10-13.) The '069 patent contains several sets of regioisomer pairs with swapped 4- and 5-positions of

12. Mylan also emphasizes language in a May 1990 article titled "The Discovery of Potent Nonpeptide Angiotensin II Receptor Antagonists" by Duncia et al., which noted that the 4-position may be substituted with either a lipophilic chlorine atom or a neutral hydrogen atom "to yield compounds of essentially equivalent binding affinity." (DTX 125, at JA 4169 n.17.) At most, this statement can be construed to indicate that a neutral—and not hydrophilic— substituent could lead to compounds with "equivalent binding affinity."

the imidazole ring—the 7711 Series and the Tetrazole Series. (Timmermans 4/16/09 Tr. JA 1338:13-17.)

The Tetrazole Series contains the data and structure of two regioisomer pairs that use a biphenyl tetrazole at the 1-position, including losartan and its regioisomer Example 118.

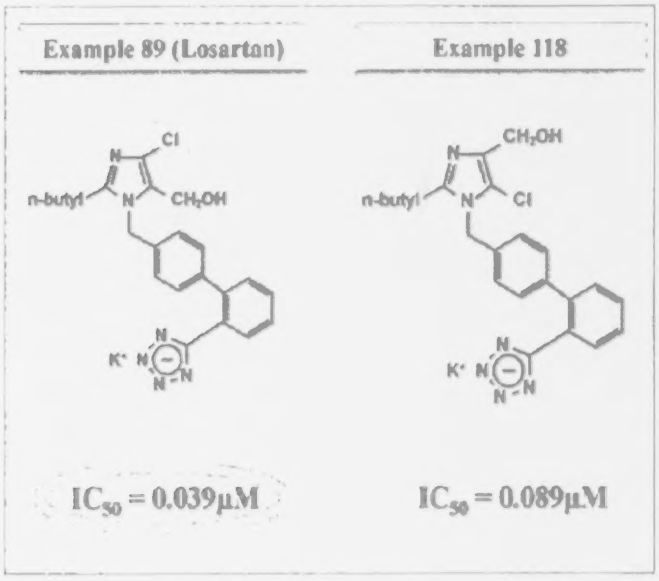

Figure 6 The Tetrazole Series. (PTX 627, at JA 25113.)

In this set, losartan exhibited better in vitro activity than Example 118, as demonstrated by lower IC_{50} values. (*Id.*) Losartan exhibited a binding affinity of 0.039 mg/kg, while the hydrophilic Example 118 showed a binding affinity of 0.089 mg/kg. (*Id.*) Likewise, in the 7711 Series, Example 94 and Example 102 both contained

lipophilic substituents at the 4-position and hydrophilic substituents at the 5-position. Conversely, Examples 95 and 105 both have hydrophilic substituents at the 4-position and lipophilic substituents at the 5-position. (*Id.*) In both sets, the compound with the lipophilic substituent at the 4-position had a lower IC_{50} value, and thus better activity.

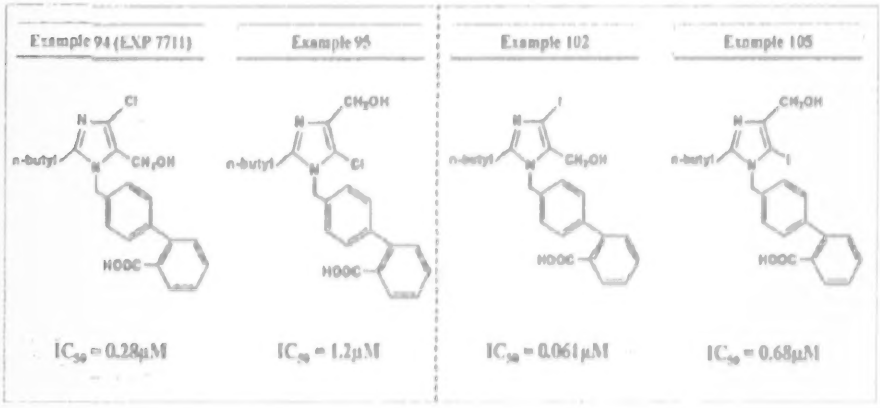

Figure 7 The 7711 Series. (PTX 626, at JA 25112.)

Example 94 exhibited a binding affinity of 0.28 mg/kg, while its regioisomer, Example 95, had a binding affinity of 1.2 mg/kg. Example 102 possessed a binding affinity of 0.061 mg/kg, while its regioisomer, Example 105, had a binding affinity of 0.68 mg/kg. (*Id.*)

Mylan refutes Daiichi Sankyo's regioisomeric analysis by reference to a July 1990 article titled "Nonpeptide Angiotensin II Receptor Antagonists" by Johnson et al. ("Johnson Article"). (PTX 224, at JA 10708.) The Johnson Article concluded that the

"electron withdrawing" substituent at the 4-position would be useful in increasing oral activity, while the substituent at the 5-position may be "capable of hydrogen bonding." (*Id.*) Mylan maintains that in each regioisomeric pair cited above, the compounds with the greater binding affinity possessed an electron withdrawing substituent at the 4-position and a substituent capable of hydrogen bonding at the 5-position. (PTX 624-25, at JA 25110-111; DTX 132, at JA 4255.) After swapping the substituents at the 4-and 5-positions, Mylan claims that the substituent at the 4-position was not electron withdrawing and the substituent at the 5-position was not capable of hydrogen bonding, thereby lowering binding affinities. Mylan's interpretation, however, is contradicted by express language of the '069 patent discussed above. The '069 patent states: "In all series examined, the more rapidly eluted [more lipophilic] isomer of a given pair has a greater biological potency than the less rapidly eluted [less lipophilic] isomer." (PTX 195, at 10093.)

c. Other Second Generation ARB Compounds

Beyond DuPont's extensive ARB work, research related to other second generation compounds evidenced the advantage of a lipophilic group at the 4-position of the imidazole ring. L-158,809, the Eisai compounds, candesartan cilexetil, and valsartan all used losartan as a lead and contain a lipophilic substituent at the 4-position or the 4-position's equivalent. (Lipinski 4/20/09 Tr. JA 1562:21-1563:3.) Dr. Weinstock even

admitted that researchers, working prior to olmesartan medoxomil's priority date, "followed the teaching of lipophilicity at the 4-position" to discover irbesartan with a lipophilic 4-position. (Weinstock 4/6/09 Tr. JA 533:6-534:4.)

Mylan points to other second generation compounds as described in an October 1992 non-prior art patent review titled "Angiotensin-II Antagonists: Patent Activity since the Discovery of DuP 753" by Peter Bühlmayer, as evidence that second generation compounds used hydrophilic substituents at the 4-position. (PTX 167, at JA 9848-879.) However, for purposes of the teaching away doctrine, only publications which qualify as prior art references may be considered. *See In re Gurley*, 27 F.3d at 553 (stating that a "reference" teaches away "when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant.") Even assuming that this article qualifies as prior art, the majority of the compounds in this paper contain a lipophilic group at the 4-position. (PTX 167, at JA 9848-879.) The publication identifies "best known" compounds, which list prior art compounds containing lipophilic groups. (*Id.*; Lipinski 4/20/09 Tr. JA 1585:15-1586:7.) The one exception is eprosartan, which employs a neutral substituent hydrogen (H) at the 4-position. (Lipinski 4/20/09 Tr. JA 1586:8-1587:4; PTX 712, at JA 25191.)

When viewed in total, the express language of the '069 patent, DuPont's development of its second generation ARB compounds, DuPont's SAR, and the structure of other second generation compounds indicate that the prior art showed more than a general preference for lipophilic groups at the 4-position. Based on this prior art, the Court finds that a person of ordinary skill would have been discouraged from using a hydrophilic substituent at this position.

D. Differences between the Claimed Subject Matter and Prior Art

Turning to the third *Graham* factor, the Court must examine the differences between the claimed subject matter and prior art. When the patent at issue involves a chemical compound, the differences between the claimed invention and the prior art often "turn[] on the structural similarities and differences between the claimed compound and the prior art." *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1356-57 (Fed. Cir. 2008). "[S]tructural similarity between claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." *Takeda*, 492 F.3d at 1356. "[I]t remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." *Id.* at 1357 (citation omitted); *see also Proctor & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009); *Eisai Co.*, 533 F.3d at 1357.

The requisite motivation can come from any number of sources and need not necessarily be explicit in the art. *Eisai Co.*, 533 F.3d at 1357 (citing *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007)). Instead, "it is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship . . . to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old." *Id.* at 1357 (quoting *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc)).

1. *Selection of Lead Compound*

An obviousness argument based on structural similarity between claimed and prior art compounds "depends on a preliminary finding that one of ordinary skill in the art would have selected [the prior art compound] as a lead compound." *Takeda*, 492 F.3d at 1357; *see also Eisai Co.*, 533 F.3d at 1359 (stating that "post-*KSR*, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound" in the prior art). The prior art may point to more than a "single lead compound for development efforts." *Altana Pharma AG v. Teva Pharms. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009). Even so, a compound will be found non-obvious if "the prior art disclose[s] a broad selection of compounds any one of which could have been selected as a lead for further investigation." *Takeda*, 492 F.3d at 1359-60.

Appendix B

A lead compound is defined as a compound with known properties that a medicinal chemist uses as a starting point for drug development. (Weinstock 3/31/09 Tr. JA 84:5-85:12.) When selecting a lead point for development, a medicinal chemist of ordinary skill considers a multitude of factors, including the lead compound's potency. (Lipinski 4/20/09 Tr. JA 1582:12-19; Weinstock 3/31/09 Tr. JA 87:25-88:4.) In addition, a medicinal chemist looks for compounds with robust packages of real data, such as binding activity, intravenous activity, oral activity, specificity, and multiple species testing. (Lipinski 4/20/09 Tr. JA 1561:10-1562:10; PTX 703-1, at JA 25172.)

Turning to the instant matter, Mylan maintains that a person of ordinary skill in the art would have selected the six compounds from the '902 patent as leads. (Weinstock 3/31/09 Tr. JA 127:2-21.) The company contends the '902 patent represented a continuation of DuPont's work on losartan and other '069 patent compounds, as evidenced by the fact that the '902 patent explicitly stated that the most preferred compounds "exhibit[ed] remarkable and unexpected potency as antihypertensives" with "oral antihypertensive activity approximately 2 to 4 fold higher than the most active compounds [of the '069 patent] which have been tested." (DTX 96, at JA 3748.) Mylan asserts that a person of ordinary skill in the art would have selected the '902 patent compounds to take advantage of the "wealth" of SAR data from structurally similar '069 patent compounds and would have been confident in the safety of the '902 patent compounds since losartan was in

clinical trials. (Lipinski 4/20/09 Tr. JA 1686:23-24; Weinstock 3/31/09 Tr. JA 127:2-21.)

Even accepting these arguments as true, Mylan has not established by clear and convincing evidence that a person of ordinary skill would have selected the '902 patent compounds out of the numerous other second generation ARBs disclosed in the prior art.[13] At the time of olmesartan medoxomil's priority date, the public had access to substantial data related to L-158,809, DuP 532, the Eisai compounds, and valsartan. Merck and DuPont released data related to the binding affinity, intravenous activity, oral activity, and selectivity of L-158,809 and DuP 532. (Lipinski 4/20/09 Tr. JA 1570-77.) Eisai disclosed data relating to the Eisai compounds' binding affinity and intravenous activity, and Ciba-Geigy revealed information about valsartan's binding affinity, intravenous activity, and oral activity. (*Id.* at JA 1577-81.) In contrast, DuPont failed to report any additional data related to the '902 patent compounds. (*Id.* at JA 1566-69.)

Moreover, even if the '902 patent compounds exhibited "antihypertensive activity approximately 2 to

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13. Although irrelevant in light of the legal standard for obviousness, the Court notes that Daiichi Sankyo did not and could not have used the '902 patent compounds as potential lead compounds because the '902 patent's priority date of February 1, 1991 pre-dated the '599 patent, which covered olmesartan medoxomil, by a mere two months. When developing olmesartan medoxomil, Daiichi Sankyo selected losartan as a lead compound, and not the '902 patent compounds.

4 fold higher than the most active compounds" of the '069 patent, this improvement is at most comparable to other second generation ARBs. In terms of binding affinity, L-158,809 had 180 times, Example 7 of the Eisai compounds had 100 times, DuP 532 had seven times, and valsartan had two times the potency of losartan. (Lipinski 4/20/09 Tr. JA 1571:7-11, 1580:18-21.) DuP 532 even evidenced three times the oral activity of losartan and L-158,809 expressed almost perfect bioavailability. (*Id.* at JA 1576:24-1577:2.) Based on this data, Dr. Weinstock admitted on cross-examination that L-158,809 and DuP 532 were significantly more potent than losartan. (Weinstock 4/6/09 Tr. JA 529:10-531:9.)

The '902 patent compounds were not the only second generation ARBs that could rely on the "wealth" of DuPont's SAR data. Just like the '902 patent compounds, DuP 532 shared losartan's imidazole-biphenyl-tetrazole backbone. (*Id.* at JA 1677:12-14.) A person of ordinary skill who chose DuP 532 or the '902 patent compounds as leads would have had access to this data when developing an antihypertensive equivalent to olmesartan medoxomil. (*Id.* at JA 1686:23-24.)

In light of the foregoing, Mylan has failed to prove by clear and convincing evidence that a person of ordinary skill in the art would have selected the '902 patent compounds over other second generation ARBs. Since a person of ordinary skill in the art could have selected a lead compound from a "broad selection of compounds," Mylan has failed to establish its prima facie case of obviousness.

Appendix B

2. *Structural Differences between Lead Compound and Olmesartan Medoxomil*

Even assuming that Mylan established by clear and convincing evidence that a medicinal chemist of ordinary skill would have selected the '902 patent compounds as leads, these compounds differ structurally from olmesartan medoxomil in several respects.

At the 4-position of the imidazole ring, the '902 patent compounds employ various branched alkyls, including an ethyl, methyl, t-butyl, and isopropyl. Olmesartan medoxomil uses a hydroxyisopropyl. (DTX 356-A, at JA 5143.) The various alkyls in the '902 patent compounds belong to the alkane class of compounds and enjoy lipophilic properties. (Lipinski 4/20/09 Tr. JA 1589:22-25, 1626:5-1627:3.) Hydroxyisopropyl, found in olmesartan medoxomil, is formed by adding a hydroxyl (OH) to an isopropyl, transforming the lipophilic alkane isopropyl into a hydrophilic alcohol.[14] (*Id.* at JA 1624:24-1626:9.)

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14. Mylan seeks to rely upon Daiichi Sankyo's second supplemental interrogatory response to argue that the hydroxyisopropyl at the 4-position of olmesartan medoxomil is lipophilic. Daiichi Sankyo's interrogatory response outlines that it would not be obvious to modify the examples of the '902 patent to get to olmesartan medoxomil because:

> [T]here was no reason in the art to substitute the alkyl group on the 4-position of the imidazole ring in Example 6 of the '902 patent with a tertiary alcohol group as used on Olmesartan Medoxomil. Alkyl and alcohol groups are different families of substituents

(Cont'd)

This change results in opposing chemical properties. The lipophilic alkanes found in the '902 patent compound possess low solubility in water and lack the ability to form hydrogen bonds. (PTX 719, at JA 25196.) Conversely, the hydrophilic hydroxyisopropyl used in olmesartan medoxomil forms hydrogen bonds and exhibits high solubility in water. (*Id.*) The character of the alkyl and alcohol groups remain constant in both small and large compounds. (Lipinski 4/20/09 Tr. JA 1627:5-9.) As recognized by the patent examiner of olmesartan medoxomil, the addition of the hydroxyl was a "critical" structural difference, which distinguished olmesartan medoxomil from the '902 patent compounds. (PTX-4, at JA 8846.)

(Cont'd)

> with entirely different properties. The prior art taught away from using a group like a tertiary alcohol at the 4-position of the imidazole ring. Preferred groups for the imidazole 4-position were lipophilic and electron-withdrawing. Changing an alkyl group at the 4-position of the imidazole ring to the tertiary alcohol group changes the properties of the resulting compounds. For example, olmesartan's tertiary alcohol group at the 4-position of the imidazole ring is capable of hydrogen bonding with the angiotensin II receptor, and is *weakly lipophilic*.

(DTX 340, at JA 5111) (citations omitted) (emphasis added). The Court finds that the phrase suggesting that the hydroxyisopropyl group itself is "weakly lipophilic" is a mistake, as evidenced from the rest of the interrogatory response.

Appendix B

Mylan maintains that the '902 patent compounds and olmesartan medoxomil were structurally similar at the 4-position by virtue of intramolecular hydrogen bonding.[15] (Weinstock 4/6/09 Tr. JA 534:13-20.) This bonding caused the hydroxyisopropyl to act like a lipophilic alkane, creating a structure similar to the '902 patent compounds. Even assuming that such intramolecular bonding occurred, Dr. Weinstock admitted that the '902 patent compounds and olmesartan medoxomil would differ under such circumstances. Intramolecular hydrogen bonding would transform olmesartan at the 4-and 5-positions of the imidazole ring. (Weinstock 4/6/09 Tr. 52:25-53:3; Yanagisawa 4/17/09 Tr. 84:8-19.) This bonding would create a new ring structure that "would certainly differ in structure from losartan . . . and the '902 compounds." (Weinstock 4/6/09 Tr. 53:4-10; Lipinski 4/20/09 Tr. 66:20-67:1; PTX 725.)

Moreover, at the time of olmesartan medoxomil invention, a person of ordinary skill in the art would not have conceived of this type of bonding. Dr. Yanagisawa's post-priority date paper titled "Nonpeptide Angiotensin II Receptor Antagonists: Synthesis, Biological Activities, and Structure-Activity Relationships of Imidazole-5-carboxylic Acids Bearing Alkyl, Alkenyl, and Hydroxyalkyl Substituents at the 4-Position and Their Related Compounds" was the first paper in the ARB art to mention intramolecular hydrogen bonding. Dr.

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15. Intramolecular hydrogen bonding refers to a situation where a hydrogen bond forms within the molecule. (Lipinski 4/20/09 Tr. 1608:17-18.)

Yanagisawa speculated that this type of bonding "might account for the potent activities of and the compounds having a hydroxyalkyl group at the 4-position." (PTX 26, at JA 9555.) If a person of ordinary skill used a hydrophilic group to act as a lipophilic group, such a decision would not have been obvious to a person skilled in the art. Instead, such a decision would have been "pretty inventive." (Lipinski 4/20/09 Tr. JA 1613:15-20.)

Turning to the 5-position of the imidazole ring, olmesartan medoxomil and the '902 patent compounds also differ. Olmesartan medoxomil is a prodrug that contains a carboxylic acid linked to a medoxomil ester at this position. (Lipinski 4/20/09 Tr. JA 1616:1-2.) Unlike olmesartan medoxomil, Examples 1, 2, and 6 of the '902 patent compounds use a carboxylic acid at the 5-position, while Examples 3, 4, and 5 employ an aldehyde (CHO). (*Id.* at JA 1616:1-2.) Notably, in 1994, DuPont attempted to create a medoxomil prodrug for Example 2 of the '902 patent compounds, resulting in a three-fold decrease in oral activity. (Hieble 4/7/09 Tr. JA 765:14-766:25; Timmermans 4/16/09 Tr. JA 1397:16-1398:1.) DuPont's failed attempt at transforming Example 2 into a prodrug highlights the significant difference in overall structure between olmesartan medoxomil and the '902 patent compounds.

3. *Reason or Motivation to Make the Specific Modifications Necessary to Achieve Olmesartan Medoxomil*

Assuming that the '902 patent compounds would have been selected as lead compounds and that a

structural similarity existed between the '902 patent compounds and olmesartan medoxomil, Mylan still fails to prove by clear and convincing evidence that a person of ordinary skill in the art would have been motivated to modify the 4-and 5-positions of the '902 patent compounds to derive the invention at issue.

a. Motivation to Make a Specific Modification to the 4-position of the Imidazole Ring

Mylan argues that a medicinal chemist of ordinary skill would have been motivated to modify the lipophilic alkyls found at the 4-position of the '902 patent compounds based on a compound revealed in the '069 patent, Example 118. Besides being the regioisomer of losartan, Example 118 was one of the "more potent" compounds in the '069 patent. (Timmermans 4/17/09 Tr. JA 1532:10-14.) Example 118 employed a hydrophilic hydroxymethyl substituent at the 4-position of the imidazole ring and a chlorine at the 5-position. (DTX 356-A, at JA 5151.)

According to Mylan, a person of ordinary skill would have changed the 4-position of the '902 patent compounds, because the '902 patent taught that the 4-position did not require electron-withdrawing substituents by virtue of the fact that these compound employed non-electron withdrawing branched alkyls. (Weinstock 4/1/09 Tr. JA 216:11-17; Yanagisawa 4/17/09 Tr. JA 1467:17-1468:4.) This contradicted the Johnson Article's teaching, which stated that an electron

withdrawing substituent at the 4-position *may* improve oral absorption. (DTX 132, at JA 4255.) Based on this contradiction, Mylan argues that a person of ordinary skill would have scanned DuPont's SAR from the '069 patent and deduced that a non-electron withdrawing substituent such as olmesartan medoxomil's hydroxyisopropyl was needed at the 4-position. This medicinal chemist of ordinary skill then would have utilized bioisosterism or the "principal of minor modifications" to transform the alkyls of the '902 patent compounds into a hydroxyisopropyl.[16]

This argument fails for several reasons. First, as discussed above, the prior art taught away from the use of a hydrophilic substituent, such as a hydroxyisopropyl, at the 4-position. When the prior art teaches a preference for substituents with opposite properties, the invention at issue is not obvious. *See Eisai Co.*, 533 F.3d at 1355-57 (finding a chemical compound non-obvious where the invention at issue replaced a more lipophilic substituent with a less lipophilic substituent in contravention of the prior art's teaching that lipophilicity at a particular position on a ring structure conferred beneficial results). Since the prior art taught

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16. Since Mylan asserts in its post-trial brief that Dr. Weinstock's testimony related to the "principal of minor modification" and bioisosterism "was not intended to substitute for the explicit motivation provided by Example 118, the Court will not address arguments raised by Daiichi Sankyo involving whether the "principal of minor modification" or bioisosterism provided an independent motivation to modify the 4-position of the imidazole ring. (Def. Post-Tr. Br. 21.)

away from the use of a hydrophilic substituent at the 4-position, a person of ordinary skill would not have been motivated to change the lipophilic alkyls in the '902 patent compounds to the hydrophilic hydroxyisopropyl found in olmesartan medoxomil.

Second, a person of ordinary skill in the art would not select the '902 patent compounds as leads only to disregard one of their distinguishing characteristics, specifically their increased lipophilicity at the 4-position. The Federal Circuit has found that a chemical compound is not obvious when the "record . . . shows no discernible reason for a skilled artisan to begin with [a lead] only to drop the very feature . . . that gave this advantageous property [for which the lead was selected.]" *Id.* at 1358. As described above, Mylan contends that a person of ordinary skill in the art would have selected the '902 patent compounds over other second generation compounds, since these compounds exhibited "oral antihypertensive activity approximately 2 to 4 fold higher than the most active compounds [of the '069 patent] which have been tested." (DTX 96, at JA 3748.) Both parties acknowledge that the branched alkyls at the 4-position of the '902 compounds were more lipophilic than the chlorine found at the 4-position of losartan and Dr. Weinstock emphasized the importance of lipophilic type binding forces in the '902 patent compounds. (Weinstock 4/1/09 Tr. JA 219:19-220:17.) He explicitly stated that "lipophilicity is . . . an important part of this patent." (Weinstock 4/1/09 Tr. JA 218:17-19.) If a person of ordinary skill would have selected the '902 patent compounds over other potential leads

because of their increased potency, the Court finds it illogical to conclude that the same hypothetical person would then quickly turn around and modify the 4-position to achieve the patent at issue. A person of ordinary skill would not alter an "advantageous part" of the '902 patent compounds for a hydrophilic substituent with opposing chemical properties. Such a decision would lack an obvious basis to one skilled and the art, and only could be considered non-obvious in light of the record presented at trial.[17]

b. Motivation to Make a Specific Modification to the 5-position of the Imidazole Ring

There is also scant evidence that a person of ordinary skill would be motivated to modify the 5-position of the '902 patent compounds to a carboxylic acid linked to a medoxomil acid. While Examples 2 and 6 of the '902 patent compounds contain a carboxylic acid, Examples 1, 3, 4, and 5 contain an aldehyde. (PTX 701, at JA 25170; DTX 96, at JA 3751.)

The '902 patent compounds exhibited a preference for an aldehyde at the 5-position. Two out of the three

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17. Even if a person of ordinary skill looked to modify the 4-position, it would have likely been to form other alkanes, alkenes, or alkynes. As admitted by Dr. Weinstock, if a lead has an alkyl group, a reasonable medicinal chemist would attempt to lengthen, shorten, branch, or make more rigid the alkyl group to derive compounds with improved properties. (Weinstock 4/6/09 Tr. JA 542:13-21.)

most preferred compounds in the '902 patent compounds use an aldehyde and not a carboxylic acid, suggesting to a person of ordinary skill that "there was something good" about this substituent. (Lipinski 4/20/09 Tr. JA 1615:17-21.) Dr. Lipinski opined that "based on first principals" you would expect better oral activity with the aldehyde, as opposed to the carboxylic acid. (*Id.* at JA 1615:22-25.)

Even if a person of ordinary skill focused on Examples 2 and 6, which contained a carboxylic acid at the 5-position, Mylan does not establish by clear and convincing evidence that such a person would have been motivated to transform the '902 patent compounds into a prodrug. When designing prodrugs, medicinal chemists overcome a whole series of "hurdles." (PTX 718, at JA 25195.) Pharmaceutical companies "avoid prodrugs" because "there are problems in . . . determining whether the prodrug itself has pharmacology" and "whether the conversion of the prodrug to [the] active [form] is reproducible." (Hieble 4/7/09 Tr. JA 761:21-763:1.) As of April 26, 1991, medicinal chemists approached the creation of a prodrug as a "last resort," "a desperation, last-ditch approach," which was unpredictable. (Lipinski 4/20/09 Tr. JA 1623:2-5.)

Moreover, if a person of ordinary skill would have employed a prodrug, there is little evidence that such a person would have selected the promoiety medoxomil. As acknowledged by Mylan's expert Dr. J. Paul Heible, medicinal chemists infrequently use medoxomil. (Hieble 4/7/09 Tr. JA 761:10-12.) While Daiichi Sankyo employed

medoxomil in various other antihypertensives and antibiotics, there is no evidence in the prior art that medicinal chemists successfully applied medoxomil in the ARB context prior to olmesartan medoxomil. Indeed, in 1994, DuPont attempted to make a medoxomil prodrug for Example 2 of the '902 patent, and failed. Adding the medoxomil ester to Example 2 resulted in a compound three times less potent than Example 2 itself. (*Id.* at JA 765:14-766:25; Timmermans 4/16/09 JA 1397:16-1398:1; PTX 175, at JA 9910.)

4. *Reasonable Expectation of Obtaining Olmesartan Medoxomil's Properties*

Additionally, Mylan has not proven by clear and convincing evidence that a person of ordinary skill in the art would have had a "reasonable expectation of success" in obtaining olmesartan medoxomil's properties. *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007); *Proctor & Gamble*, 566 F.3d at 996. In *KSR Intern. Co. v. Teleflex Inc.*, 550 U.S. 398, 402 (2007), the Supreme Court stated that when an obvious modification "leads to the anticipated success," the invention is likely the product of ordinary skill and is obvious. "[O]bviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer*, 480 F.3d at 1364 (citing *In re Corkill*, 771 F.2d 1496, 1500 (Fed. Cir. 1985)).

Here, a person of ordinary skill in the art would not have "reasonably expected" that modifying the 4-

position of the imidazole ring from a lipophilic to a hydrophilic substituent would have lead to increased oral activity and binding affinity. The prior art taught that a lipophilic alkyl group at the 4-position provided better potency than a hydrophilic hydroxyalkyl group at the same position. (Lipinski 4/20/2009 Tr. JA 1625:12-15.) Based on this teaching, a person of ordinary skill would have expected olmesartan medoxomil to exhibit decreased binding activity and decreased oral activity even when compared to first generation ARBs like losartan. Instead, olmesartan medoxomil displayed high activity in binding affinity tests when administered intravenously and orally. In terms binding affinity, olmesartan medoxomil exhibited 470 times the potency of losartan. For oral and intravenous activity, olmesartan medoxomil showed 40 times the potency intravenously and 100 times the potency orally when compared to losartan. (PTX 26, at JA 9556, PTX 63, at JA 9676, PTX 676, at JA25164; Hieble 4/7/09 Tr. JA 672:8-19; Fink 4/16/09 Tr. JA 1238:9-1239:16.) Since the '902 patent compounds "exhibit[ed] remarkable and unexpected potency as antihypertensives" when compared to losartan, a person of ordinary skill would have also expected reduced activity from compounds with a hydrophilic group at the 4-position of the '902 patent compounds. (DTX 96, at JA 3748; Lipinski 4/20/2009 Tr. JA 1628:7-11.)

In total, Mylan has failed to establish a prima facie case of obviousness. Mylan has not proven by clear and convincing evidence that a person of ordinary skill would have selected the '902 patent compounds as lead, that

the '902 patent compounds are structurally similar to olmesartan medoxomil, that a person of ordinary skill would have been motivated to modify the 4-and 5-positions of the imidazole ring, or that a person of ordinary skill would have reasonably expected to obtain olmesartan medoxomil's properties. As such, Claim 13 of the '599 patent, which covers olmesartan medoxomil, is not invalid for obviousness.

E. Secondary Considerations of Non-Obviousness

Assuming *arguendo* that Mylan established a prima facie case of obviousness, secondary considerations further mitigate against a finding of obviousness. Objective indicia of non-obviousness include: (1) unexpected results; (2) commercial success; (3) long felt, unmet need; (4) copying; and (5) industry praise and recognition for the inventions. *Graham*, 383 U.S. at 17. Secondary considerations extend beyond what was known at the time of the invention and may include later discovered unexpected properties of the invention. *Knoll Pharm. Co., Inc. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004).

When reaching the ultimate conclusion of obviousness, courts rely on secondary considerations as part of the "totality of the evidence." *Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1483 (Fed. Cir. 1997). These considerations often represent "the most probative and cogent" evidence in the record. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983). Even so, "they do not control the

obviousness conclusion." *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988). As demonstrated by Daiichi Sankyo, several secondary considerations weigh against a finding of obviousness, specifically unexpected results and commercial success.

1. *Unexpected Results*

Evidence of "unexpected results" allows a patent-holder to rebut a prima facie case of obviousness by showing that the "claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected." *In re Soni*, 54 F.3d at 750. The reasoning behind this secondary consideration is straightforward: "that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious." *In re Mayne*, 104 F.3d 1339, 1343 (Fed. Cir. 1997). To qualify as unexpected, the claimed properties or results must be different in "kind and not merely in degree" from the results of the prior art. *In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996). "[W]hen unexpected results are used as evidence of non-obviousness, the results must be shown to be unexpected compared with the closest prior art."[18] *In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991).

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18. As discussed above, Mylan has not established by clear and convincing evidence that the '902 patent compounds would have been selected by a person of ordinary skill as "lead compounds." Even so, for purposes of this section, the Court will consider the '902 patent compounds as the closest prior art.

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Daiichi Sankyo contends that olmesartan medoxomil exhibited unexpected blood pressure lowering ability as compared to the '902 patent compounds. More precisely, the patent holder argues that olmesartan medoxomil showed an unexpected result by lowering blood pressure one to two millimeters of mercury (mm Hg) more than the other ARBs on the market. Whether or not olmesartan medoxomil lowers blood pressure unexpectedly more is subject to some dispute between the parties. The Court need not address this issue, however, since it finds that olmesartan medoxomil exhibits unexpected results as compared to the '902 patent compounds in terms of potency, drug-drug interactions, insurmountable antagonism, inverse agonism, and other rehabilitative properties.

With regards to potency, a medicinal chemist of ordinary skill would have considered a two to four fold increase in intravenous and oral potency over the '902 patent compounds as unexpected. (Fink 4/16/09 Tr. JA 1237:14-21.) The '902 patent explicitly states that the most preferred compounds "exhibit[ed] *remarkable and unexpected potency* as antihypertensives" and have "oral antihypertensive activity approximately 2 to 4 fold higher than the most active compounds [of the '069 patent] which have been tested." (DTX 96, at JA 3748) (emphasis added). If the '902 patent compound exhibited "remarkable and unexpected" potency in relation to compounds from '069 patent with a two to four fold increase, then the same baseline applies to a comparison between olmesartan medoxomil and the '902 patent compounds. (Weinstock 3/31/09 Tr. JA 119:24-120:12.)

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As demonstrated at trial, olmesartan medoxomil exhibited roughly 2 to 2.5 the *in vivo* activity of Examples 2 and 6 of the '902 patent compounds respectively. (Fink 4/16/09 Tr. JA 1239:5-10; PTX 26, at JA 9552.) Orally, the claimed compound showed a three-fold increase in potency over Examples 2 and 6 of the '902 patent.[19] (Hieble 4/7/09 Tr. JA 752:24-753:4.)

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19. Mylan challenges these findings by arguing that these differences in *in vivo* activity and oral potency are irrelevant because Daiichi Sankyo neglected to submit data related to Examples 1, 3, 4, and 5 of the '902 patent compounds. However, Daiichi Sankyo need "need not test compounds taught in each and every reference" to rebut a prima facie case of obviousness. Rather, there must be sufficient evidence "to permit a conclusion respecting the relative effectiveness of applicant's claimed compounds and the compounds of the closest prior art." *In re Johnson*, 747 F.2d 1456, 1461 (Fed. Cir. 1984) (citing *In re Payne*, 606 F.2d 303, 316 (CCPA 1979)). In the instant matter, there is sufficient evidence to conclude that Examples 2 and 6 represent the relative effectiveness of all the '902 patent compounds. First, although not structurally similar, Examples 2 and 6 are the closest in terms of chemical structure to olmesartan medoxomil. (PTX 701, at JA 25170.) While neither compound is a prodrug, both compounds employ a carboxylic acid at the 5-position of the imidazole ring. Example 6 of the '902 patent compound only differs from olmesartan, the active metabolite of olmesartan medoxomil, by one oxygen atom at the 4 position. (Lipinski 4/20/09 Tr. JA 1626:2-4.) Second, DuPont singled out Example 2 as one of three preferred compounds in the '902 patent. Even though the other two preferred '902 patent compounds contain an aldehyde at the 5-position, which Daiichi Sankyo acknowledged would be expected to exhibit better oral activity, the '902 patent explicitly states that Example 2, as a preferred compound, exhibited "remarkable and unexpected" oral antihypertensive properties over the '069 patent compounds. (*Id.* at JA 1615:12-16; PTX 530, at JA 24999.)

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When compared to the '902 patent compounds, olmesartan medoxomil possessed a substantially lower likelihood of drug-drug interactions. Drug-drug interactions constitute a "serious event," which may cause the removal of a commercial drug from the market. (Hieble 4/7/09 Tr. JA 699:20-23; Fink 4/16/09 Tr. JA 1264:2-7). Daiichi Sankyo presented evidence that the compound was found to be four to seven times less likely to inhibit the cytochrome P450 family of enzymes found in the liver than Examples 2 and 6 of the '902 patent compounds. (Fink 4/16/09 Tr. JA 1268:6-17.) This lack of inhibition reduced the risk of potentially deadly drug-drug interactions.

Olmesartan medoxomil also qualifies as an insurmountable antagonist. The patented compound has been shown to bind to the AII receptor in such a manner that "it cannot be displaced by angiotensin no matter how high the concentration of angiotensin." (Hieble 4/7/09 Tr. JA 693:5-15.) At "a given concentration of 0.3 nanomolar, olmesartan suppresses the response at 100 nanomolar [of angiotensin II] greater than example 6" of the '902 patent. (Hieble 4/7/09 Tr. JA 696:17-20.) At this concentration, olmesartan is completely insurmountable, while Example 6 of the '902 patent lacks this ability. (Hieble 4/7/09 Tr. 697:6-15.)

Not only does olmesartan medoxomil exhibit insurmountable antagonism, but the active metabolite olmesartan possesses higher inverse agonist activity than Example 6 of the '902 patent compounds. (Fink 4/16/09 Tr. JA 1260:19-1261:1.) Inverse agonism refers

to the property of an ARB to reduce or eliminate the baseline activity of the AT_1 receptor. (Hieble 4/7/09 Tr. JA 690:9-13.) Inverse agonism represents "a potentially very important property of ARBs [] [b]ecause of a conundrum"— hypertensive patients generally "do not have higher levels of the renin angiontensin system activity" compared to "normal patients." (Fink 4/16/09 Tr. JA 1257:7-1258:4). ARBs qualifying as inverse agonists might "work more effectively in the patients who have low levels of [] renin angiotensin system activity." (Fink 4/16/09 Tr. 1258:2-4.) As admitted by Dr. Hieble, "olmesartan had statistically-significant inverse agonism activity in the wild type receptor, and example 6 of the '902 patent had no significant effect." (Hieble 4/7/09 Tr. JA 691:13-18.)

As compared to other second generation ARBs and the '902 patent compounds, olmesartan medoxomil displayed other rehabilitative properties. In particular, olmesartan medoxomil increases renin secretion, providing the highly desirable effect of stimulating the AT2 receptor. The drug reduces atherosclerotic plaque volume, which helps to lower plaque volume toward normal levels in hypertensive patients. (Carey 4/14/09 Tr. JA 1049:23-1053:15, 1053:24-1055:13.) Olmesartan medoxomil shows an ability to reverse damage to kidney tissue, as well as damage to vascular walls, and causes a "highly significant reduction in wall-to-lumen ratio," bringing this ratio "back to the level of [a] healthy normal control." (*Id.* at JA 1057:18-1061:24.)

2. ***Commercial Success***

Besides unexpected results, evidence of an invention's commercial success may present strong evidence of non-obviousness. *See, e.g.*, *Demaco Corp. v. F. Von Langsdorff Licensing, Ltd.*, 851 F.2d 1387, 1391 (Fed. Cir. 1988). Commercial success is "usually shown by significant sales in a relevant market." *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1377 (Fed. Cir. 2000). However, evidence showing sale of a large number of goods supposedly embodying the claimed invention does not necessarily demonstrate non-obviousness. The success must be due to the claimed features of the invention, rather than factors such as advertising, superior workmanship, or other features within the commercialized technology. *Pfizer Inc. v. Teva Pharms. USA, Inc.*, 461 F. Supp. 2d 271, 274 (D.N.J. 2006) (citing Roger Schechter & John Thomas, *Principles of Patent Law* 164).

Here, the record indicates that olmesartan medoxomil, as commercialized in Benicar and the two combination products Benicar HCT and Azor ("Benicar products"), is a commercial success. Since its introduction in 2002, Benicar products have enjoyed total net sales of over $3.1 billion and total gross sales over $4 billion. Benicar products have grown from yearly net sales of $18.9 million in 2002 to $909 million in 2008. (PTX 590-1, at JA 25092.) Doctors have written over 58 million prescriptions for the Benicar products, steadily growing from 378,426 in 2002 to 14,856,487 in 2008. (PTX 593, at JA 25096.) Benicar and Benicar HCT

rank in the top 5% of U.S. prescription drugs in terms of sales. (PTX 652, at JA 25153.)

Although the seventh ARB in its class to hit the market, Benicar products gained market share at the expense of its competitors. Benicar's market share has grown to over 16.6%, making it the third largest available ARB. (PTX 583, at JA 25088.) Mylan's marketing expert, Harry Boghigian, opined at trial that Benicar's growth curve is "similar" to the "extremely nice growth curve" for Diovan, the market leader, as demonstrated by the dotted lines below:

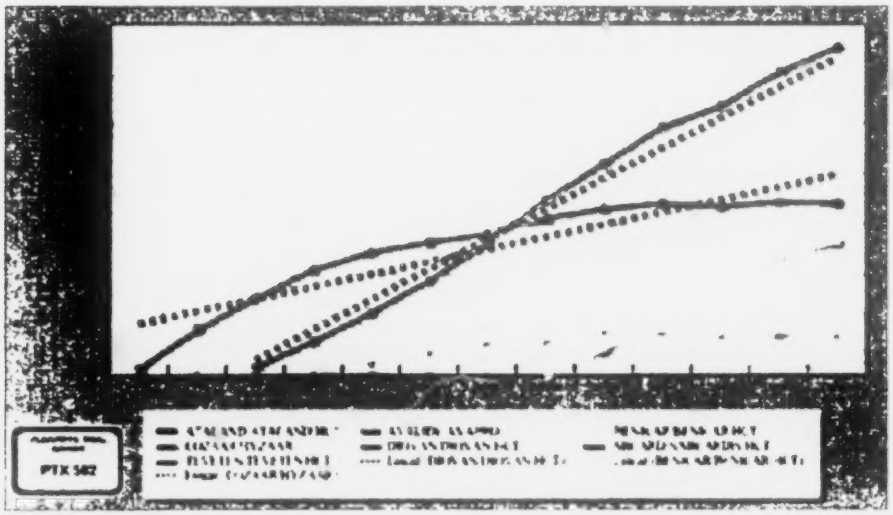

Figure 8 Linear Growth of Benicar/Benicar HCT in Comparison to Diovan/Diovan HCT and Cozaar/Hyzaar 1995-2007. (PTX 582, at JA 25087; Boghigian 4/8/09 Tr. JA 935:5-9.)

This growth is telling especially when compared to Tevetan, the last ARB to hit the market prior to Benicar. In the approximate two years prior to Benicar's launch, Tevetan gained little traction, managing to capture a mere 0.29% of the ARB market. (PTX 583, at JA 25088.)

The Benicar products not only gained market share, they vastly exceeded the internal pre-launch forecasts of Daiichi Sankyo. The cumulative net sales of the Benicar family nearly double Daiichi Sankyo's predictions. In 2005, Daiichi Sankyo expected $265 million in net sales, while earning $447.2 million. (PTX 591, at JA 25093.) By 2008, the projections of Daiichi Sankyo differed by over $500 million. For 2008, Daiichi Sankyo estimated net sales of $345 million and earned $909.5 million. (*Id.*)

The Benicar products success was also recognized by major managed care organizations. These drugs have achieved "preferred" status on formularies of at least seven of the fourteen major managed care organizations. (Smith 4/14/09 Tr. JA 1144:8-20; PTX 662, at JA 25160.) By contrast, Avapro, which has been on the market for eight years, achieved "preferred" status on only six of fourteen major formularies, and Cozaar, the first commercialized ARB, achieved "preferred" status on nine of fourteen major formularies. (PTX 662, at JA 25160.)

Mylan argues that Benicar's success stems not from its properties, but from Daiichi Sankyo's marketing and advertising efforts. However, Daiichi Sankyo spent

roughly the same amount in marketing the Benicar products as its competitors. (PTX 579-1, at JA 25083.) Daiichi Sankyo utilized a smaller sales force than other pharmaceutical companies to sell the Benicar family of drugs and Daiichi Sankyo's ratio of brand marketing expenses to sales for olmesartan medoxomil fails to illustrate pervasive marketing. (Boghigian 4/8/09 Tr. JA 951:16-952:8.) For example, in 2007, Daiichi Sankyo's ratio of brand marketing expenses to net sales for Benicar products was 39%, consistent with industry practice. (*Id.* at JA 952:7-8.) Moreover, there is no evidence that Daiichi Sankyo offered excessive discounts or rebates to managed care organizations or Medicare and Medicaid programs or that Daiichi Sankyo priced Benicar products out of line with other ARBs on the market. (*Id.* at JA 954:4-6; PTX 264, at JA 10989.)

Mylan also asserts that certain "false or misleading" promotional materials led to Benicar's commercial success. In January 2006, the FDA sent a warning letter to Daiichi Sankyo regarding certain promotional materials for Benicar, based on material excerpted from published studies comparing the efficacy of ARBs at starting doses. (DTX 310, at JA 5053-77.) After Daiichi Sankyo ceased using this material and sent corrective letters to physicians, the sales from Benicar products continued to increase. (Boghigian 4/8/09 Tr. JA 970:2-973:3, 985:12-15.) Even after the FDA letter, physicians rated Benicar as the best, or among the best, ARBs in the market. (Smith 4/14/09, at JA 1156:13-1160:13; PTX 284, at JA 11579.)

Finally, Mylan contends that olmesartan medoxomil cannot be considered a commercial success because Daiichi Sankyo did not earn a profit from the sale of Benicar products. Mylan asserts "it's highly unlikely" that the Benicar products demonstrated profitability, based on Daiichi Sankyo's profit and loss statements. (Boghigian 4/8/09 JA 888:23-889:17.) As an initial matter, "profitability analysis has a number of issues with it . . . it's subject to a lot of internal accounting conventions that are unique to a particular company." (Smith 4/14/09 Tr. JA 1116:17-22.) A comparison of profits with competing products is difficult, since "[m]ost companies report profitability at a company level." (*Id.* at JA 1117:13-14.)

After considering the evidence in the record, the Court finds that Daiichi Sankyo profited from sale of Benicar products. There is sufficient evidence that the Benicar products earned between $250 and $300 million a year in "direct controllable profit," after accounting for sales forces expenses and the profit sharing relationship with its co-promoter, Forest Pharmaceuticals Inc. ("Forest Laboratories.") (Smith 4/14/09 Tr. JA 1146:1-8.) This range is supported by the Benicar products reported net income for 2008 of $270 million. (PTX 650, at JA 25132-151; Smith 4/14/09 Tr. 1151:21-1152:4, 1204:13-17.)

Profitability is also demonstrated by the payments made to Forest Laboratories under the parties' co-promotion agreement. Under this arrangement, Daiichi Sankyo provided Forest Laboratories a 45% profit-split

in exchange for the co-promotion of Benicar. (Boghigian 4/8/09 JA 881:25-883:6, JA 955:22-956:2.) In profit and loss statements, Daiichi Sankyo reported payments to Forest Laboratories as "co-promotion expenses," which increased as sales of the Benicar products increased. (Boghigian 4/8/09 JA 954:22-956:19.) A review of Forest Laboratories' annual reports confirms that Daiichi Sankyo made payments to its co-promoter. Daiichi Sankyo began paying Forest Laboratories when the product reached cumulative profitability in 2005. (Boghigian 4/8/09 Tr. JA 905:12-16; Smith 4/14/09 Tr. JA 1147:19-1148:1.)

Accordingly, even if Mylan established a prima facie case of obviousness, the commercial success of the Benicar family and the unexpected results exhibited by olmesartan medoxomil over the '902 patent compounds and other second generation ARBs weigh towards a finding of non-obviousness.[20]

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20. Daiichi Sankyo also argues that other secondary considerations weigh towards a finding of non-obviousness, such as long-felt, unmet need, industry praise and recognition, and copying. At trial, Daiichi Sankyo neglected to present sufficient evidence indicating that olmesartan medoxomil addressed a real, commercial demand for purposes of establishing a long-felt, unmet need. Similarly, Daiichi Sankyo has not presented evidence of copying, except to claim that Mylan's filing of its ANDA constitutes copying and has offered no credible evidence of industry acclaim. Although Dr. Yanagisawa briefly referenced an award from the Pharmaceutical Society of Japan, it is not clear whether the award was for Benicar or for Dr. Yanagisawa's contributions to medicinal chemistry during the course of his long career. (Yanagisawa 4/17/09 Tr. JA 1455:15-1457:7.)

Appendix B

III. CONCLUSIONS OF LAW

For the foregoing reasons, the Court finds that Mylan has failed to prove by clear and convincing evidence that the '599 patent is obvious under 35 U.S.C. § 103(a). As a result, the '599 patent is neither invalid nor unenforceable. Mylan has infringed on the '599 patent under 35 U.S.C. § 271(e)(2). An appropriate Order accompanies this Opinion.

s/William J. Martini
William J. Martini, U.S.D.J.

APPENDIX C — ORDER OF THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF NEW JERSEY DATED JULY 30, 2009

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

Civ. Nos. 06-3462, 07-3039, and 08-2752

DAIICHI SANKYO COMPANY, LIMITED
and DAIICHI SANKYO, INC.,

Plaintiffs and
Counterclaim Defendants,

v.

MYLAN PHARMACEUTICALS INC.,
MYLAN LABORATORIES INC., MATRIX
LABORATORIES, LTD., and MYLAN, INC.,

Defendants and
Counterclaim Plaintiffs.

ORDER

HON. WILLIAM J. MARTINI

This matter coming before the Court to resolve the question of whether Claim 13 of United States Patent No. 5,616,599 ("the '599 patent") is invalid by reason of obviousness; and the Court having heard the testimony of expert witnesses and having considered the

documentary evidence and depositions submitted by the parties; and having reviewed the pretrial and post-trial briefs of the parties, and for the reasons set forth in the accompanying Opinion,

IT IS this 30th day of July, 2009 hereby,

ORDERED that Claim 13 of the '599 patent is not obvious under 35 U.S.C. § 103(a). Mylan has infringed on the '599 patent under 35 U.S.C. § 271(e)(2).

/s/
William J. Martini, U.S.D.J.